3-year scoping report

Topic: Management of osteoporosis and the prevention of fragility fractures: SIGN 142 (2015)

Background

The purpose of this scoping is to identify any information that may be relevant to the key questions of the guideline (SIGN 142) on the management of osteoporosis and the prevention of fragility fractures.

A rapid high-level search of the literature was conducted using a predefined list of resources. The search focused on secondary sources of evidence (health technology assessments, evidence-based guidelines, systematic reviews and meta-analyses) and was limited to evidence published, in English language, since 2014.

The results of the evidence review, in section 2, are based mainly on information contained within the executive summaries or abstracts of the evidence identified. A comprehensive assessment and critical analysis of the evidence was not carried out.

The results of the review were discussed by Ailsa Stein, Programme Manager, SIGN, and Professor Stuart Ralston, Chair of SIGN 142: management of osteoporosis and the prevention of fragility fractures, to identify the priorities for review listed in section 1. The review and proposed updates were circulated to the original guideline development group, and three other relevant healthcare professionals for comment (see section 3).

Conclusion

While there is evidence for additional risk factors, it is not possible to include everything which could be considered a potential risk. The focus of the update should be on areas with additional adverse effects and new pharmacological therapies. The SCOOP study should also be considered as it has the potential to change practice.

Decision

The recommendation to update the guideline was ratified by the Guideline Programme Advisory Group on 6 June 2018.
The Guideline Programme and Advisory group agreed that a revision of SIGN 142 should be scheduled into the SIGN programme. The following areas should be prioritised for update:

- SCOOP screening tool
- Zolpidem use and osteoporosis risk
- Safety of denosumab
- New pharmacological therapies (abaloparatide, bazedoxifene, teriparatide, romosozumab)
- Vitamin D supplementation
- Removal of the sections on cyclical etidronate and strontium ranelate.

Section 1: Proposed action from the scoping summary

Section	Details of update	KQ	Priority
Section 3.4 (Risk factors)	Bhardwaj A et al. Treatment for osteoporosis in people with ß-thalassaemia. Cochrane Database of Systematic Reviews, 2016. A section on ß-thalassaemia should be added.	Addition to Kq 1	Desirable
Section 3.5 (Pharmacological risk factors)	Dynamed Plus. Osteoporosis causes and risk factors. 2017 Increased risk of osteoporosis with use of zolpidem	Addition to KQ1	Essential
Section 3.5.13 (Pharmacological risk factors: glucocorticoids)	Hansen, KE et al. A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children. Seminars in Arthritis and Rheumatism 44 (2014) 47–54 This adds evidence in children and could be included in an update.	Kq 1 Original question is in adults	Desirable
Section 3.5.14	Risk of osteoporotic fracture may be increased with use of insulin, sulfonylureas, or thiazolidinediones, but not metformin or sitagliptin. This section should be updated to include evidence on sitagliptin.	Addition to Kq 1	Desirable
Section 6.3.2 Dietary-derived calcium	There is new evidence, from observational data, of harm from high milk consumption which should be included in the guideline.	Kq 1	Desirable
Sections 6.3.3 and 6.4.14 (Vitamin D supplementation)	Vitamin D. There is new evidence emerging, so this section should be reviewed.	Kq 4	Desirable
Sections 6.4.6 and 6.4.10 (Denosumab)	Zhou, Z et al. Safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density: a meta-analysis. Cochrane Database of Systematic Reviews, 2014. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guañabens N, Obermayer-Pietsch B, Ralston SH, Eastell R, Zillikens MC. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone. 2017 Dec;105:11-17. (This reference is additional to the scoping search)	Kq 4	Essential

	Lee, SH et al. Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis. Osteoporos Int (2014) 25:1131–1139 Update section on adverse effects. May lead to a new recommendation to advise patients of risks.		
New pharmacological therapies: Bazedoxifene	Ellis, AG et al. Bazedoxifene versus oral bisphosphonates for the prevention of nonvertebral fractures in postmenopausal women with osteoporosis at higher risk of fracture: a network meta-analysis. Value in health 17 (2014) 424 – 432 This is a new pharmacological therapy so should be included, although it is not widely used.	Addition to Kq 4	Desirable

Additional evidence suggested for inclusion by Professor Stuart Ralston:

Section	Details of update	KQ	Priority
Section 4 (Diagnostic tools and monitoring)	Add evidence from SCOOP study. SCOOP study: Turner DA, Khioe RFS, Shepstone L, Lenaghan E, Cooper C, Gittoes N, Harvey NC, Holland R, Howe A, McCloskey E, O'Neill TW, Torgerson D, Fordham R; SCOOP Study Team. The Cost-Effectiveness of Screening in the Community to Reduce Osteoporotic Fractures in Older Women in the UK: Economic Evaluation of the SCOOP Study. J Bone Miner Res. 2018 Feb 22. doi: 10.1002/jbmr.3381. [Epub ahead of print] Conclusion: women at high risk of hip fracture based on FRAX probability are responsive to appropriate osteoporosis management. McCloskey E, Johansson H, Harvey NC, Shepstone L, Lenaghan E, Fordham R, Harvey I, Howe A, Cooper C, Clarke S, Gittoes N, Heawood A, Holland R, Marshall T, O'Neill TW, Peters TJ, Redmond N, Torgerson D, Kanis JA; SCOOP Study Team. Management of Patients With High Baseline Hip Fracture Risk by FRAX Reduces Hip Fractures-A Post Hoc Analysis of the SCOOP Study. J Bone Miner Res. 2018 Feb 26. Conclusion: The current study demonstrates that a systematic, community-based screening program of fracture risk in older women in the UK represents a highly cost-effective intervention. Shepstone L, Lenaghan E, Cooper C, Clarke S, Fong-Soe-Khioe R, Fordham R, Gittoes N, Harvey I, Harvey N, Heawood A, Holland R, Howe A, Kanis J, Marshall T, O'Neill T, Peters T, Redmond N, Torgerson D, Turner D, McCloskey E; SCOOP Study Team. Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. Lancet. 2018 Feb 24;391(10122):741-747. Conclusion: Systematic, community-based screening programme of fracture risk in older women in the UK is feasible, and could be effective in reducing hip fractures.	Kq 2	Essential
New pharmacological	**Abaloparatide vs teriparatide. RCT. (Still to be licensed)** Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P,	Additions to Kq 4	Essential

therapies	Zerbini CAF, Hu M, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C, . Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With OsteoporosisA Randomized Clinical Trial. JAMA. 2016;316(7):722–733. **Teriparatide superior to risedronate in vertical fractures.** Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, Lespessailles E, Minisola S, Body JJ, Geusens P, Möricke R, López-Romero P. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2017 Nov 9. pii: S0140-6736(17)32137-2. **Romosozumab** Liu Y, Cao Y, Zhang S, Zhang W, Zhang B, Tang Q, Li Z, Wu J. Romosozumab treatment in postmenopausal women with osteoporosis: a meta-analysis of randomized controlled trials. Climacteric. 2018 Apr;21(2):189-195. There are also a number of RCTs on romosozumab versus alendronate.		Abaloparatide and Romosozumab are awaiting licensing and have not been considered by the Scottish Medicines Consortium.
Sections for removal	**Section 6.4.5 Cyclical etidronate** **Section 6.4.7 Strontium ranelate** These drugs have been withdrawn from the market.		Desirable

Additional changes suggested by peer reviewers:

Section 3.4.6	As a smaller issue there is now evidence accruing that HIV and some anti-retroviral therapies might be associated with an increase in fracture risk. [Osteoporos Int. 2018 Mar;29(3):595-613. Reduced bone mineral density in human immunodeficiency virus-infected individuals: a meta-analysis of its prevalence and risk factors. Goh SSL(1), Lai PSM(2), Tan ATB(3), Ponnampalavanar S(4). A meta-analysis was conducted to evaluate the prevalence of osteopenia/osteoporosis in human immunodeficiency virus (HIV)-infected individuals. The prevalence of osteopenia/osteoporosis in HIV-infected and antiretroviral therapy (ART)-treated individuals was significantly higher than respective controls. Evidence regarding bone loss within first year of HIV infection or ART initiation was preliminary. PURPOSE: The aim of the study is to systematically review published literature on the prevalence of osteopenia/osteoporosis and its associated risk factors in HIV-infected individuals. METHODS: A literature search was conducted from 1989 to 2015 in six databases. RESULTS: Twenty-one cross sectional and eight longitudinal studies were included. The prevalence of osteopenia/osteoporosis was significantly higher in both HIV-infected [odds ratio (OR) = 2.4 (95%CI: 2.0, 2.8) at lumbar spine, 2.6 (95%CI: 2.2, 3.0) at hip] and ART-treated individuals [OR = 2.8 (95%CI: 2.0, 3.8) at lumbar spine, 3.4 (95%CI: 2.5, 4.7) at hip] when compared to controls. PI-treated individuals had an OR of 1.3 (95%CI: 1.0, 1.7) of developing osteopenia/osteoporosis compared to controls. A higher proportion of tenofovir-treated individuals (52.6%) had lower BMD compared to controls (42.7%), but did not reach statistical significance (p = 0.248). No significant difference was found in the percent change of BMD at the lumbar spine, femoral neck, or total hip from baseline to follow-up between HIV-infected, PI-treated, tenofovir-treated, and controls. Older age, history of bone fracture, low BMI, low body weight, being Hispanic or Caucasian, low testosterone level, smoking, low CD4 cell count, lipodystrophy, low fat mass, and low lean body mass were associated with low BMD. CONCLUSIONS: The prevalence of osteopenia/osteoporosis in HIV-infected and antiretroviral therapy (ART)-treated individuals was two times more compared to controls. However, evidence concerning bone loss within the first year of HIV infection and ART initiation was preliminary. The guideline currently states that there is insufficient evidence to determine whether	Kq 1	Desirable

	HIV infection itself predisposes to fractures independently of drug treatments and other confounding factors.]		
Section 6.4.6	**Bisphosphonate use and the risk of atypical femoral fracture** 'The only area I think may be considered for updating would be regarding atypical femoral fractures and bisphosphonate use. I have attached some references that may be relevant (the 2010 would not be picked up but I was not sure if this was included in previous reviews). I understand the limitation regarding this area is the lack of evidence, but I think it certainly is an area that requires some attention if possible.' Refs: N Engl J Med. 2010 May 13;362(19):1761-71. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. Black DM[1], Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, Cauley J, Leung PC, Boonen S, Santora A, de Papp A, Bauer DC; Fracture Intervention Trial Steering Committee; HORIZON Pivotal Fracture Trial Steering Committee. Fam Pract. 2015 Jun;32(3):276-81. Increased risk for atypical fractures associated with bisphosphonate use. Lee S[1], Yin RV[2], Hirpara H[2], Lee NC[2], Lee A[2], Llanos S[3], Phung OJ[4]. Acta Orthop. 2015 Feb;86(1):100-7. Risk of atypical femoral fracture during and after bisphosphonate use. Schilcher J[1], Koeppen V, Aspenberg P, Michaëlsson K. [The risk is discussed in section 6.4.6 but the conclusion is that the benefit outweigh the risk. This is also the conclusion of Adler et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for bone and mineral research. Journal of bone and mineral research, Vol. 31, No. 1, January 2016 (see KQ5, Section 2)]	Kq 4	Low

Section 2: Summary of evidence by key questions

Topic: Management of osteoporosis and the prevention of fragility fractures: SIGN 142 (2015)

Date of search: 15/01/18

Prepared by: Hilda Emengo

Key concepts: osteoporosis, osteo*, fragil*, fracture, fragility fracture, bone, bone density, bone mineral, bmd, fragility, prevention, management

KQ 1: What factors contribute to increased fracture risk/increased number of fractures?

Reference and study type*	Information likely to be relevant	Impact on guideline
BMJ Best Practice. Hip fractures. 2016 Best practice*	**Summary** • Occurs predominantly in the elderly. The risk increases significantly with age. • Associated most commonly with low-energy injury (e.g., fall from standing height) and osteoporosis or osteopenia. • Treatment is most commonly surgical. The choice of implant depends on the fracture pattern and the surgeon's preference.	Exclude – focus is on hip fracture
Lassemillante, AC et al. Prevalence of osteoporosis in prostate cancer survivors II: a meta-analysis of men not on androgen deprivation therapy. Cochrane Database of Systematic Reviews, 2015.	This review is an update to a previous review (Lassemillante, AC et al. 2014) identified in this scoping. The meta-analysis investigated evidence on the bone health of hormone-naïve prostate cancer patients compared with the bone health of men with prostate cancer on androgen deprivation therapy (ADT). The pooled prevalence of osteoporosis, low bone mass and normal bone mass were estimated for and compared with similar subgroups from a previously published meta-analysis. Overall, men with prostate cancer were found to experience poor bone health prior to treatment with ADT.	Section 3.5.9 Recommendation: Men over the age of 50 with prostate cancer, who are taking GnRH agonists may be considered for fracture-risk assessment, particularly in the presence of other risk factors. It was felt that this is adequately covered.

Reference and study type*	Information likely to be relevant	Impact on guideline
Systematic review and meta-analysis*	The prevalence of osteoporosis varied from 4 to 38 % in hormone-naïve prostate cancer patients and results showed that men with more advanced disease have a higher prevalence of osteoporosis. Men with prostate cancer on ADT have poorer bone health than their hormone-naïve counterparts. The review recommends that all men with prostate cancer should have regular bone health monitoring, irrespective of ADT treatment, in order to prevent or reduce morbidity associated with osteoporosis.	
Lassemillante AM et al. Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. Endocrine (2014) 45:370–381 DOI 10.1007/s12020-013-0083-z Systematic review and meta-analysis*	The review evaluated the prevalence of osteoporosis prostate cancer survivors undergoing androgen deprivation therapy. Findings from that meta-analysis showed that the prevalence of osteoporosis varies between 9 and 53 % and is partly explained by the site of osteoporosis measurement, ethnicity, disease stage and treatment duration. The review concluded that the results highlight the high prevalence of osteoporosis in prostate cancer survivors and supports use of preventative approaches as a component of their usual care.	**Section 3.5.9** Recommendation: Men over the age of 50 with prostate cancer, who are taking GnRH agonists may be considered for fracture-risk assessment, particularly in the presence of other risk factors. It was felt that the existing recommendation is adequate.
Hansen, KE et al. A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children. Seminars in Arthritis and Rheumatism 44 (2014) 47–54	The review assessed the effects of systemic glucocorticoid therapy on bone mineral density (BMD) and fractures in children ≤18 years. The review identified 16 relevant studies, including 10 BMD (287 children) and six fracture (37,819 children) studies. The evidence suggest that children treated with glucocorticoid therapy have lower spine BMD compared with healthy children. Spine BMD was significantly lower (-0.18; 95% CI = -0.25; -0.10 g/cm^2) in children receiving glucocorticoid therapy, compared with matched healthy	**Section 3.5.13** Recommendation: Patients taking oral glucocorticoids should be considered for fracture-risk assessment. This adds evidence in children which should be included in an update.

Reference and study type*	Information likely to be relevant	Impact on guideline
Systematic review and meta-analysis*	controls (for age and gender). Spine BMD was also lower in children taking glucocorticoids, compared with children with the same disease not taking glucocorticoids (-0.14; 95% CI = -0.27; 0.00 g/cm^2). The incidence of clinical fracture varied between 2% and 33%, while the incidence and prevalence of morphometric vertebral fracture ranged from 6% to 10% and 29% to 45% respectively.	
Lopez LM et al. Steroidal contraceptives: effect on bone fractures in women. Cochrane Database of Systematic Reviews, 2014. Systematic review*	The review utilised data from 19 RCTs to examine the effect of using hormonal contraceptives before menopause on the risk of fracture in women. Of these, 11 trials examined different combined oral contraceptives (COCs) or regimens of COCs; five compared an injectable versus another injectable, implant or IUD; two assessed implants and one compared the transdermal patch versus the vaginal ring. BMD was assessed in 17 trials, 12 studies measured biochemical markers of bone turnover and no study assessed fracture. Depot medroxyprogesterone acetate (DMPA) resulted in reduced bone mineral density (BMD). BMD increased with DMPA plus estrogen supplement and decreased with DMPA plus placebo supplement in the placebo-controlled trials. Some COC formulations appeared to have more positive effects than others but did not have negative effects on BMD. Results were inconsistent across all implant evaluations. Single-rod etonogestrel implants were associated with a greater decrease in BMD compared with two-rod levonorgestrel implants. Based on the evidence identified, the review concluded that it was difficult to determine the effect of steroidal contraceptives on fracture risk. Overall, the evidence was considered to be of moderate quality due to the small numbers of participants and large losses in some of the trials.	**Section 3.5.8** Recommendation: Women using long-term (for at least two years) depot medroxyprogesterone acetate should be advised that treatment can reduce bone density but that the effects reverse when treatment is stopped and the overall risk of fracture is low. This is an update to the Cochrane review cited in the guideline. It does not alter the recommendation.

KQ 2: Which diagnostic measurements or tools are effective in identifying increased risk of fracture?

Reference and study type*	Information likely to be relevant	Impact on guideline
NICE Medtech innovation briefing [MIB 106] (2017): Bindex for investigating suspected osteoporosis Brief report*	**Summary** The brief describes a portable pulse-echo ultrasound device (Bindex) used to aid decision making on the investigation and treatment of osteoporosis. The Bindex is pocket sized and can be connected to and used with any laptop or desktop computer's USB socket. Compared with axial dual-energy X-ray absorptiometry (DXA), the Bindex makes measurements of the tibia with thresholds of 90% sensitivity and specificity. Bindex is aimed to be used alongside current algorithmic fracture risk assessment tools (FRAX or QFracture). If these suggest an intermediate or high risk of osteoporosis fracture, Bindex could be used to determine whether referral for DXA scan is needed (in the case of confirmed intermediate risk) or not (if low risk). Treatment could be considered for those at high fracture risk or high risk for osteoporosis as measured with Bindex. The evidence was obtained from two diagnostic accuracy studies (1 US and 1 Finnish), including 1,127 women in primary care. The studies demonstrated reasonable agreement for osteoporosis risk when determined in women with intermediate risk using FRAX and Bindex compared with FRAX and DXA. However, there are no prospective studies showing the effect of Bindex on the need for DXA scans and data on the correlation between tibial bone thickness and femoral bone mineral density is limited. The cost of Bindex includes the cost of the device and the software licensing needed (a licence per computer varies by number of analyses needed: £4,000 for 300 analyses, £6,000 for 500 analyses and £10,000 for 1,000 analyses).	**Section 4** Bindex not included in guideline This is not a device commonly used in clinical practice, The evidence reports no hard outcomes. There is no need to include it.

Reference and study type*	Information likely to be relevant	Impact on guideline
ACR Appropriateness Criteria® osteoporosis and bone mineral density. American College of Radiology, 2016. Clinical guideline*	**Recommendations** • DXA (dual x-ray absorptiometry) is the primary diagnostic choice by which to screen women >65 years of age and men >70 years of age for osteoporosis. • DXA is indicated in postmenopausal women <65 years of age with additional risk factors for fracture. • DXA is the primary diagnostic choice by which to follow patients' BMD (bone mineral density). • VFA (vertebral fracture assessment) represents a useful screening study to identify patients at risk whose BMD may be above treatment thresholds. • QCT (quantitative computed tomography) can be utilised to evaluate baseline and follow-up BMD. • Patients on long-term bisphosphonate therapy who present with thigh or groin pain should be imaged bilaterally with radiography followed by MRI. • Extended-femoral-view DXA is not a substitute for femoral radiography in the setting of thigh or groin pain in long-term bisphosphonate patients. **Appropriateness criteria** **Variant 1:** Asymptomatic BMD screening or individuals with established or clinically suspected low BMD. • All women age 65 years and older and men age 70 years and older (asymptomatic screening) • Women younger than age 65 years who have additional risk for osteoporosis, based on medical history and other findings. Additional risk factors for osteoporosis include: o Estrogen deficiency o A history of maternal hip fracture that occurred	**Section 4** Recommendation: Fracture-risk assessment should be carried out, preferably using QFracture, prior to DXA in patients with clinical risk factors for osteoporosis and in whom antiosteoporosis treatment is being considered. VFA and QCT are not included in the guideline. This guidance does not differ significantly from what SIGN recommends. No change needed. The evidence on VFA is unlikely to impact on practice.

Reference and study type*	Information likely to be relevant	Impact on guideline
	after the age of 50 years o Low body mass (<127 lb or 57.6 kg) o History of amenorrhea (>1 year before age 42 years) • Women younger than age 65 years or men younger than age 70 years who have additional risk factors, including: o Current use of cigarettes o Loss of height, thoracic kyphosis • Individuals of any age with bone mass osteopenia or fragility fractures on imaging studies such as radiographs, CT, or MRI • Individuals age 50 years and older who develop a wrist, hip, spine, or proximal humerus fracture with minimal or no trauma, excluding pathologic fractures • Individuals of any age who develop 1 or more insufficiency fractures • Individuals being considered for pharmacologic therapy for osteoporosis • Individuals being monitored to: o Assess the effectiveness of osteoporosis drug therapy o Follow up medical conditions associated with abnormal BMD **Variant 2:** Vertebral Fracture Assessment VFA is a feature of DXA scanners in which lateral thoracic and lumbar spine images are obtained and screened for fracture. The detection of fractures in some patients with low bone mineralisation is a predictor of future fractures and allows for their risk restratification and potential initiation of pharmacotherapy.	

Reference and study type*	Information likely to be relevant	Impact on guideline
	Indications for VFA include patients with T-scores less than −1.0 and 1 or more of the following: • Women age ≥70 years or men age ≥80 years • Historical height loss >4 cm (>1.5 inches) • Self-reported but undocumented prior vertebral fracture • Glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months **Variant 3:** Follow-up. Patients demonstrated to have risk for fracture of low density. **Variant 4:** Identify low BMD. Premenopausal females with risk factors. Males 20 to 50 years of age with risk factors. • Individuals with medical conditions that could alter BMD, such as: o Chronic renal failure o Rheumatoid arthritis and other inflammatory arthritides o Eating disorders, including anorexia nervosa and bulimia o Organ transplantation o Prolonged immobilisation o Conditions associated with secondary osteoporosis, such as gastrointestinal malabsorption or malnutrition, sprue, osteomalacia, vitamin D deficiency, endometriosis, acromegaly, chronic alcoholism or established cirrhosis, and multiple myeloma o Individuals who have had gastric bypass for obesity. The accuracy of DXA in these patients	

Reference and study type*	Information likely to be relevant	Impact on guideline
	might be affected by obesity o Individuals with an endocrine disorder known to adversely affect BMD (e.g., hyperparathyroidism, hyperthyroidism, or Cushing syndrome) • Individuals receiving (or expected to receive) glucocorticoid therapy for >3 months • Hypogonadal men older than 18 years and men with surgically or chemotherapeutically induced castration • Individuals beginning or receiving long-term therapy with medications known to adversely affect BMD (e.g., anticonvulsant drugs, androgen deprivation therapy, aromatase inhibitor therapy, or chronic heparin) **Variant 5:** Follow-up to Low BMD. Premenopausal Females with Risk Factors. Males 20 to 50 Years of Age with Risk Factors **Variant 6:** Diagnosis. Males and females >50 years of age with advanced degenerative changes of the spine with or without scoliosis. **Variant 7:** Suspected fracture (nonscreening) of a vertebral body based on acute or subacute symptomatology in a patient with suspected osteoporosis or a patient treated with corticosteroids (>3 months). First examination. **Variant 8:** Suspected fracture (nonscreening) of a vertebral body based on acute or subacute symptomatology in a patient with suspected osteoporosis or a patient treated with corticosteroids (>3 months). Initial radiograph is negative. **Variant 9:** Patients on long-term treatment (3–5 years) of	

Reference and study type*	Information likely to be relevant	Impact on guideline
	bisphosphonates with thigh or groin pain. First examination. **Variant 10:** Patients on long-term treatment (3–5 years) of bisphosphonates with thigh or groin pain and negative radiographs. Atypical fracture recognition is critical to patient treatment. **Major features**: • The fracture is associated with minimal or no trauma, as in a fall from a standing height or less. • The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur. • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. • The fracture is noncomminuted or minimally comminuted. • Localised periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring"). **Minor features**: • Generalised increase in cortical thickness of the femoral diaphysis • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral incomplete or complete femoral diaphysis fractures • Delayed fracture healing	

Reference and study type*	Information likely to be relevant	Impact on guideline
ACR Appropriateness Criteria® osteonecrosis of the hip. American College of Radiology, 2015. Clinical guideline*	**Recommendations and appropriateness criteria** **Variant 1: Adult or child. Clinically suspected osteonecrosis. First study.** The initial imaging study in either an adult or child with clinically suspected osteonecrosis should be radiography. These images must include a frog-leg lateral view. The important features of osteonecrosis can be seen only on this projection. Although radiography is not sensitive for early changes of osteonecrosis, it is the least expensive and most widely available imaging modality. **Variant 2: Adult. Clinically Suspected Osteonecrosis. Normal Radiographs or Radiographs That Show Femoral Head Lucencies Suspicious for Osteonecrosis** In the adult patient with suspected osteonecrosis of the hip and normal or suspicious radiographs but clinically requiring further radiologic assessment, MRI is the modality of choice. MRI is generally considered the most sensitive and specific radiologic method of assessment for identification of osteonecrosis, with accuracy of 97% to 100% in several series. **Variant 3: Child. Clinically Suspected Osteonecrosis. Normal Radiographs or Radiographs Suspicious for Osteonecrosis** In a child with suspected femoral head osteonecrosis with normal radiographs or radiographic evidence of osteonecrosis but in whom further evaluation is needed, MRI is the radiologic modality of choice. Similar to the adult patient, MRI is both sensitive and specific for the identification of osteonecrosis in the pediatric population **Variants 4 and 5: Adult or Child. Osteonecrosis with Femoral**	This is not directly relevant – exclude.

Reference and study type*	Information likely to be relevant	Impact on guideline
	Head Collapse by Radiographs in the Painful Hip(s). Surgery Contemplated In the adult or child patient with pain and radiographic evidence of articular collapse resulting from femoral head osteonecrosis and with surgical intervention contemplated for treatment, further imaging assessment is typically required. **Variant 6: Adult or Child. Osteonecrosis Clinically Suspected. Radiographs Normal or Abnormal but MRI Contraindicated. Further Evaluation Is Needed** The imaging assessment of a patient, adult or child, who cannot undergo MRI but requires further radiologic evaluation can be performed with either bone scintigraphy or CT. Bone scintigraphy should be performed with high-resolution pinhole collimation and is particularly useful in patients with normal radiographs.	
Wang, KC et al. Evidence-based outcomes on diagnostic accuracy of quantitative ultrasound for assessment of pediatric osteoporosis - a systematic review. Pediatr Radiol (2014) 44:1573–1587 Systematic review and meta-analysis*	Due to the limitations of dual-energy absorptiometry (DXA), this review investigated the diagnostic accuracy of quantitative ultrasound (a modality free of ionizing radiation) for assessing paediatric osteoporosis based on the U.S. Preventive Services Task Force guidelines. The review identified 28 studies (1,963 patients; 807 reported boys and 761 girls, others unspecified; mean age, 0-19 years). The quality of reporting was considered "excellent" in 86% (24/28) of studies and "adequate" in 39% (11/28) of studies. The review concluded that there is currently no evidence of the diagnostic value of quantitative ultrasound even though it provides reliable measurements.	New evidence does not impact on the guideline.

Reference and study type*	Information likely to be relevant	Impact on guideline
Nayak, S. et al. Performance of risk assessment instruments for predicting osteoporotic fracture risk: a systematic review. Osteoporos Int. 2014; 25(1): 23–49. Systematic review*	This review examined the performance of osteoporosis absolute fracture risk assessment instruments for predicting absolute fracture risk, or calibration, in populations other than their derivation cohorts. Fourteen studies with substantial heterogeneity were included. Six studies evaluated the WHO's Fracture Risk Assessment (FRAX) instrument in five separate cohorts and the remaining studies assessed a range of risk assessment instruments. Results showed that only a few studies have assessed the calibration of these instruments in populations separate from their development cohorts. About half of the studies found good instrument calibration, with fracture probabilities close to predicted probabilities for different risk categories. Mixed performance in different populations was reported in studies that evaluated the calibration of FRAX. A similar proportion of studies that evaluated simple risk assessment instruments (≤5 variables) found good calibration when compared with studies that assessed complex instruments (>5 variables). The review recommended the evaluation of the calibration of instruments in different populations prior to widespread use.	This does not provide new evidence which would impact on the guideline.
Minniti, D et al. Techniques for diagnosing osteoporosis: a systematic review of cost-effectiveness studies. International Journal of Technology Assessment in Health Care, Vol. 30, issue 3, 2014	The review investigated the cost effectiveness of dual-energy X-ray absorptiometry (DXA) alone compared with a two-step procedure with quantitative ultrasound sonography (QUS) plus DXA for identifying postmenopausal women with osteoporosis. It was difficult to determine which screening test may be more cost-effective for identifying postmenopausal women with osteoporosis. Eleven papers were identified (seven journal articles and four reports). Two papers reported that the cost per true positive case diagnosed by DXA was higher than that for diagnosis by QUS+DXA, while one paper reported a lower cost and three papers reported inconclusive results. There was	Results are inconclusive. Does not impact on the guideline.

Reference and study type*	Information likely to be relevant	Impact on guideline
Systematic review*	variation in the unit costs of the DXA and QUS tests, parameters and thresholds on the QUS and DXA tests, types of device used, the prevalence of osteoporosis as well as the sensitivity and specificity of the techniques.	

KQ 4: Which pharmacological interventions are effective in fracture prevention? (exclude phase I and II trials and studies of less than one year duration)

Reference and study type*	Information likely to be relevant	Relevance to guideline
NICE technology appraisal guidance [TA464] (2017): Bisphosphonates for treating osteoporosis Technology appraisal guidance*	**Recommendations** • Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) are recommended as options for treating osteoporosis in adults only if: o the person is eligible for risk assessment as defined in NICE's guideline on osteoporosis and o the 10-year probability of osteoporotic fragility fracture is at least 1%. • Intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended as options for treating osteoporosis in adults only if: o the person is eligible for risk assessment as defined in NICE's guideline on osteoporosis and o the 10-year probability of osteoporotic fragility fracture is at least 10% or o the 10-year probability of osteoporotic fragility fracture is at least 1% and the person has difficulty taking oral	SIGN 142 does not use 10-year probability as criteria for treatment. The new NICE TA recommendation rationale is: Oral bisphosphonates are recommended because new analyses show they are cost effective for people with at least a 1% risk of osteoporotic fragility fracture, irrespective of the assessment tool used. The results were provided when valuing a quality-adjusted life year (QALY) at £20,000 per QALY gained and at £30,000 per QALY gained. At £20,000 per QALY gained oral bisphosphonates were cost effective (that is, the incremental net benefit of bisphosphonates

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	bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium) or these drugs are contraindicated or not tolerated. • Estimate the 10-year probability of osteoporotic fragility fracture using the FRAX or QFracture risk tools, in line with NICE's guideline on osteoporosis. • The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient, or their carers, about the advantages and disadvantages of the treatments available. If generic products are available, start treatment with the least expensive formulation, taking into account administration costs, the dose needed and the cost per dose. • These recommendations are not intended to affect treatment with alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.	was positive) at: around 1% probability of fracture risk when using QFracture and any treatment threshold when using FRAX. Should the 1% probability be included in SIGN 142? No. The NICE conclusions are not supported by any evidence. Treating people with a fracture risk of 1% has the potential to cause rather than prevent fractures. Strongly disagree with this advice.
Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline.	The guideline was focused on the relapse and survival benefit of bone-modifying agents in nonmetastatic breast cancer. The guideline recognises that there is clear evidence for the use of bone-modifying agents such as bisphosphonates to reduce the risk of fragility fractures in at-risk populations and to treat metastatic cancer to the bone. None of the recommendations are intended to restrict the use of bone-modifying agents for these purposes but may influence the selection of specific	**Section 3.5.5** Recommendation: Women over the age of 50 taking aromatase inhibitors may be considered for fracture-risk assessment, particularly in the presence of other risk factors. The guideline does not have a specific section

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American Society of Clinical Oncology, 2017. Clinical guideline*	bisphosphonate when given for both bone health and adjuvant therapy. The recommendations have associated 'qualifying statements' are an integral part of the recommendations and should be read and cited together. **Recommendation 1** • It is recommended that administration of bisphosphonates as adjuvant therapy be considered for postmenopausal patients with breast cancer (including patients premenopausal before treatment who have menopause induced by ovarian suppression as detailed in Recommendation 5) deemed candidates for adjuvant systemic therapy. • The final decision of whether or not to administer bisphosphonates should be made during consultation between the patient and oncologist, taking into account patient and disease characteristics, including risk of recurrence, and weighing the potential benefits and risks (adverse effects). **Qualifying Statements for Recommendation 1** • While the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small. For patients with cancers assessed as having low risk of recurrence, the use of bisphosphonates may not result in clinically meaningful effect. • Considerations in deeming patients at high enough recurrence risk to receive adjuvant systemic therapy may also apply in deciding on bisphosphonate use. The majority of patients (83%) in the meta-analysis had also received adjuvant chemotherapy. Standard clinical and pathologic risk factors and recognized clinical tools may be	on management of women with breast cancer. This is adequately covered already. The evidence in the guideline is the American Society of Clinical Oncology's view of the same evidence base used for SIGN 142.

Reference and study type*	Information likely to be relevant	Relevance to guideline
	used, where applicable, to estimate risk of recurrence and mortality. • Risk factors for osteonecrosis of the jaw (ONJ) and renal impairment should be assessed (Recommendation 6). • Patients should receive all other recommended breast cancer treatment, including surgery, radiation, and/or systemic therapy (see, for example, the National Guideline Clearinghouse [NGC] summary of the Cancer Care Ontario [CCO] guideline Optimal systemic therapy in early breast cancer). • There is no information to guide the use of bone-modifying agents for patients receiving systemic adjuvant therapy for completely resected local recurrence. **Recommendation 2** • Zoledronic acid and clodronate are the recommended bisphosphonates for adjuvant therapy in breast cancer. • There is a need for more information comparing different agents and schedules, and it is recommended that such trials be conducted to establish the utility and optimal administration of other bisphosphonates for adjuvant therapy. **Qualifying Statements for Recommendation 2** • Preliminary data from the SWOG S0307 trial suggest that clodronate, ibandronate, and zoledronic acid may provide similar disease-free survival (DFS) and overall survival (OS) benefit. However, as these data have, to date, only been published in abstract form, no definitive recommendations regarding ibandronate can yet be made. Full publication of the SWOG S0307 trial and results of the TEAM IIb (BOOG 2006-04) trial may support adjuvant	

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	ibandronate use. There is a large difference in ibandronate dosage between these trials (50 mg/day) and that used in treating osteoporosis (150 mg/month orally or 3 mg every 3 months intravenously). This dosage difference should be considered in future comparisons. • Clodronate has not been studied specifically in patients receiving aromatase inhibitors (AIs). • While the direct evidence from adjuvant trials is considered sufficient only for zoledronic acid and clodronate, others have hypothesized that any agent proven to reduce the risk of fragility fractures in at-risk populations (e.g., patients with postmenopausal or drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer. Given orally for osteoporosis treatment, alendronate has been used daily or weekly, while risedronate and ibandronate have been used daily, weekly, or monthly. Ibandronate has also been used intravenously. Less frequent administration, compared with clodronate, may make these preferable to patients if shown to be of adjuvant benefit. Further trials with adequate power and primary outcomes of DFS and OS are required to determine the optimal agent and dosing schedule. • Different adverse effect profiles, frequency and route of administration, cost, and regulatory approval may influence selection. **Recommendation 3** • While results for adjuvant denosumab look promising, data are insufficient at this time to make any recommendation regarding its use in the adjuvant setting.	

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	• It is recommended that studies directly comparing denosumab with bisphosphonates and evaluating administration schedules be conducted. **Qualifying Statements for Recommendation 3** • While the ABCSG-18 trial studied denosumab use in postmenopausal women with hormone receptor–positive breast cancer receiving AIs and found clear fracture reduction benefit, DFS results have only been reported as a conference presentation or abstract. As survival data have, to date, only been published in abstract form, no definitive recommendations can yet be made. Results are promising but limited compared with the body of evidence for bisphosphonates. Further results of the ABCSG-18 and D-CARE trials may provide stronger evidence for adjuvant denosumab use. **Recommendation 4** • For patients who will receive adjuvant bisphosphonates (Recommendation 1), zoledronic acid at 4 mg intravenously over 15 minutes (or longer) every 6 months for 3 to 5 years or clodronate orally at 1,600 mg/day for 2 to 3 years are recommended. Different durations may be considered. • More research is recommended comparing different bone-modifying agents, doses, dosing intervals, and durations. **Qualifying Statements for Recommendation 4** • In jurisdictions where the recommendation cannot be followed due to availability, similar doses and schedules of zoledronic acid or clodronate are considered reasonable. • The optimal dose and schedule of administration of zoledronic acid and clodronate have not been determined;	

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	however, the recommended doses and schedules have been found effective in many of the adjuvant breast cancer trials and result in fewer or less severe adverse effects than regimens used in patients with metastatic disease (i.e., 4 mg zoledronic acid every 3 to 4 weeks). • The optimal duration of adjuvant bone-targeted agents has not been determined; the recommendations reflect durations found effective in the EBCTCG meta-analysis and other trials included in the literature review. It is unclear whether there is benefit to longer-term administration, although studies indicate that the benefit of bisphosphonates continues after administration is stopped due to the persistence of the drug within the bone. There are concerns about adverse effects such as atypical bone fractures based on reports from the osteoporosis literature, and some osteoporosis recommendations allow a treatment holiday from bisphosphonates after 3 to 5 years for patients with a lower risk of fracture. • Administration of clodronate for >3 years or zoledronic acid for >5 years has not been evaluated in adjuvant trials, and, therefore, a recommendation of longer duration is not supported at this time. This limitation in the evidence may be especially relevant to patients receiving long-term endocrine therapy, as the NGC summary of the CCO guideline Optimal systemic therapy in early breast cancer includes recommendations for endocrine therapy for up to 10 years based primarily on results from the ATLAS, aTTom, and MA.17 trials. • The optimal timing to start bisphosphonates after diagnosis of breast cancer is unclear; however, most of the clinical trials started soon after surgery or	

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	chemotherapy. **Recommendation 5** • For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause (at least 12 months of amenorrhea prior to initiation of chemotherapy or endocrine therapy) and menopause induced by ovarian ablation or suppression (but not the cessation of menses due to chemotherapy alone). In women age ≤60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured prior to initiation of any systemic therapy to receive adjuvant bisphosphonates. **Qualifying Statements for Recommendation 5** • As indicated in the NGC summary of the CCO guideline Optimal systemic therapy in early breast cancer, assessing menopausal status is difficult in patients age ≤60 years who experience amenorrhea secondary to chemotherapy or tamoxifen. Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with transient chemotherapy-induced amenorrhea. In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen. • Some publications have suggested that patients experiencing chemotherapy-induced amenorrhea are at high risk for adverse bone effects and may be candidates for bone-modifying agents. Evidence is insufficient to	

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	address use of these agents as adjuvant treatment in this population. **Recommendation 6** • A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible. Patients should be informed of the risk of developing ONJ, especially with tooth extractions and other invasive dental procedures. Patients should inform their dental practitioner of their treatment. Patients with suspected ONJ should be referred to a dental practitioner with expertise in treating this condition. Recent guidelines or position papers by groups such as the International Task Force on Osteonecrosis of the Jaw, the American Association of Oral and Maxillofacial Surgeons, and the American Dental Association should be consulted. • Patients should have serum calcium measured prior to starting treatment. Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function prior to starting this treatment, and for serum calcium and increase in serum creatinine throughout the treatment period. • Calcium and vitamin D supplementation is recommended unless otherwise contraindicated. Oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least 2 hours to allow for maximum absorption. • Symptoms such as ocular pain or loss of vision may be due to serious inflammatory conditions such as uveitis or	

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	scleritis and should be promptly evaluated by an ophthalmologist. **Qualifying Statements for Recommendation 6** • The risk of ONJ increases with frequency, dose, and duration of bisphosphonate administration. Risk can be reduced with appropriate screening prior to treatment and modification of dental care. Risk of ONJ when bisphosphonates are administered, as suggested in Recommendation 4, is lower than for patients receiving higher doses or more frequent administration as is used for cancers with bone metastasis. • Some organizations advise dental assessment and care prior to any cancer treatment, preferably as soon as possible after diagnosis to allow time for dental procedures and adequate healing prior to treatment. • The CCO formulary monograph for zoledronic acid recommends "comprehensive dental evaluation of both hard and soft tissues before starting bisphosphonate treatment; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment." U.S. Food and Drug Administration (FDA) prescribing information for zoledronic acid indicates that "cancer patients should maintain good oral hygiene and should have a dental examination with preventative dentistry prior to treatment with bisphosphonates." • It is unclear whether bone-modifying therapy should be withheld if invasive dental treatment is required. Some have hypothesized that withholding bone-modifying therapy may allow for better bone healing and suggested stopping treatment 2 months prior to oral surgery and delaying restarting until osseous healing has occurred.	

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	The alternative view is that a short break in bisphosphonate administration will have no effect as bone effects of bisphosphonates are maintained for years after treatment stops. • Hypocalcemia is a known adverse effect of bisphosphonate treatment, especially with the higher doses and more frequent administration given to patients with metastatic cancer. It is relatively rare (<1%) at lower doses (Recommendation 4) in patients without pre-existing conditions such as renal insufficiency and who have adequate vitamin D status and calcium intake. • There is conflicting evidence as to whether inflammatory eye conditions are directly caused by bisphosphonates or in conjunction with some underlying inflammatory disease process; however, if not treated promptly, these conditions may lead to blindness. Discontinuation of bisphosphonates may be necessary.	
Dawn K et al. Bisphosphonate therapy for osteogenesis imperfect. Cochrane Database of Systematic Reviews, 2016. Systematic review*	This review is an update of a previously published Cochrane review. The review investigated the effectiveness and safety of bisphosphonates in increasing bone mineral density, reducing fractures and improving clinical function in people with osteogenesis imperfecta. Based on 14 trials (including 819 participants and mainly at a low risk of bias), the review concluded that the available evidence was limited and demonstrates that oral or intravenous bisphosphonates increase bone mineral density in children and adults with osteogenesis imperfecta. It was unclear whether oral or intravenous bisphosphonate treatment consistently decreases fractures. It was also difficult to determine whether bisphosphonates improve clinical status (reduce pain; improve growth and functional mobility) in people with	Treatment of patients with osteogenesis imperfect is not included/relevant to the guideline. No action required.

Reference and study type*	Information likely to be relevant	Relevance to guideline
	osteogenesis imperfecta. The review recommended that more research is required in the following areas: long-term fracture reduction, improvement in quality of life, optimal method, duration of therapy and long-term safety of bisphosphonate therapy.	
Bhardwaj A et al. Treatment for osteoporosis in people with ß-thalassaemia. Cochrane Database of Systematic Reviews, 2016. Systematic review*	The review assessed the efficacy and safety of treatment for osteoporosis in people with beta-thalassaemia using data from four trials (with 211 participants, three of which were considered to have high or unclear risk of bias. Three trials examined the effect of bisphosphonate therapies and one trial examined the effect of zinc supplementation. The review concluded that there is evidence to indicate an increase in bone mineral density at the femoral neck, lumbar spine and forearm after administration of bisphosphonates and at the lumbar spine, and hip after zinc sulphate supplementation. There were no major adverse effects reported in two of the bisphosphonate trials. The neridronate trial reported a reduction in the use of analgesic drugs and back pain score in favour of bisphosphonate treatment. Adverse effects were not reported in the trial of different doses of pamidronate or the zinc supplementation trial.	Treatment of patients with beta-thalassaemia is not included in the guideline. It may be worthwhile updating the guideline to include this. Previously not common in Scotland, but populations are increasing.
Allen Cs et al. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database of Systematic Reviews, 2016. Systematic review*	The review examined the benefits and harms of bisphosphonates for the prevention and treatment of glucocorticosteroid-induced osteoporosis. The review included 27 RCTs with 3075 participants and pooled analysis for incident vertebral fractures from 12 trials (1343 participants) with high-certainty evidence and low risk of bias. The findings of the review support the use of bisphosphonates to reduce the risk of vertebral fractures and the prevention and treatment of steroid-induced bone loss. Overall, there was: high-certainty evidence that bisphosphonates are useful in reducing the risk of vertebral fractures for up to 24 months; low-certainty evidence that bisphosphonates result in	**Section 7.5** The new evidence does not change the guideline recommendations.

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	little or no difference in preventing nonvertebral fractures; moderate-certainty evidence that bisphosphonates are useful in preventing and treating corticosteroid-induced bone loss at both the lumbar spine and femoral neck and; low-certainty evidence that bisphosphonates offer little or no difference in the occurrence of serious adverse events or withdrawals due to adverse events.	
Zhou, Z et al. Safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density: a meta-analysis. Cochrane Database of Systematic Reviews, 2014. Systematic review and meta-analysis*	The meta-analysis investigated the safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density (BMD) compared with placebo or bisphosphonates. Eleven studies were identified. Results showed that overall there was no significant difference in any adverse events (AAE) when denosumab was compared with placebo or bisphosphonates (RR=0.99, 95% CI=0.98-1.01, p=0.29), serious adverse event (SAE) (RR=1.05, 95% CI=0.98-1.13, p=0.18), neoplasm/cancer (RR=1.14, 95% CI=0.95-1.37, p=0.16) and deaths (RR=0.77, 95% CI=0.57-1.04, p=0.09). There were significant differences in SAE related to infection (RR=1.23, 95% CI=1.00-1.52, p=0.05) and non-vertebral fracture (RR=0.86, 95% CI=0.74-1.00, p=0.05) when denosumab was compared with placebo or bisphosphonates. Subgroup analysis by the type of drugs used in the control group did not show any differences between denosumab and bisphosphonates in SAE related to infection (RR=1.13, 95% CI=0.63-2.03) and non-vertebral fracture (RR=1.31, 95% CI=0.87-1.98). The review concluded that denosumab treatment significantly decreased the risk of non-vertebral fracture but increased the risk of SAE related to infection in the postmenopausal women with osteoporosis or low BMD, compared to placebo.	**Section 6.4.6** Harms with denosumab are listed. Infection is not included. **Section 6.4.10** Recommendation: Denosumab is recommended to prevent vertebral, non-vertebral and hip fractures in postmenopausal women with DXA-proven osteoporosis for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with the special administration instructions. GPP: Denosumab is contraindicated in patients with hypocalcaemia and should be used with caution in patients with renal impairment. Patients who are treated with denosumab should be given calcium and vitamin D supplementation unless their dietary intake is adequate.

Reference and study type*	Information likely to be relevant	Relevance to guideline
		Hypocalcaemia is not discussed in the Cochrane Review. **Section 6.5.6** One study reported that denosumab is safe and effective for up to five years. This section needs to be updated not for efficacy but for adverse effects. (see also Tsourdi and Zillikens denosumab AEs SR).
Tadrous, M et al. Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis. Osteoporos Int (2014) 25:1225–1235 Systematic review and meta-analysis*	This review carried out a Bayesian-based network meta-analysis to investigate the comparative gastrointestinal safety of bisphosphonates. The review identified 50 studies (32 alendronate, 12 risedronate, 5 etidronate and 7 zoledronic acid) and found that Zoledronic acid had the highest probability of causing the highest number of any gastrointestinal adverse event (91%) and nausea (70%). Etidronate (70%) and zoledronic acid (28%) had the highest chance of discontinuation due to an adverse event. Among oral bisphosphonates, Etidronate had the highest chance (56%) of having the greatest number of upper gastrointestinal symptoms. There were no difference found for serious adverse events.	**Section 6.4.6** Risk of GI side effects are already in the guideline (currently unreferenced).
Reid, IR et al. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet 2014; 383: 146–55	The review examined the effects of vitamin D supplementation on bone mineral density. The review included 23 studies, involving 4082 participants (92% women, average age 59 years) and concluded that sustained widespread use of vitamin D for preventing osteoporosis in community-dwelling adults with no specific risk factors for vitamin D deficiency appears to be inappropriate. Each study measured bone mineral density at one to five sites (lumbar spine, femoral neck, total hip, trochanter, total	**Section 6.3.3** GPP: In Scotland, dietary vitamin D intakes are insufficient to meet the needs of people with inadequate sunlight exposure. Supplementation with 10 micrograms/day of vitamin D (400 IU) should be considered to

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Systematic review and meta-analysis*	body, or forearm). In ten studies (n=2294), individuals received vitamin D doses of < 800 IU per day. Only one study showed benefit at more than one site. Meta-analysis identified a small benefit at the femoral neck (weighted mean difference 0.8%, 95% CI 0.2-1.4) with heterogeneity among trials (I2=67%, p<0·00027) and no effect at any other site.	avoid deficiency. **Section 6.4.14** Calcium and vitamin D supplements may be considered to reduce the risk of non-vertebral fractures in patients who are at risk of deficiency due to insufficient dietary intake or limited sunlight exposure. This is an area with new research emerging so may require an update.
Mandema, JW et al. Time course of bone mineral density changes with denosumab compared with other drugs in postmenopausal osteoporosis: a dose-response–based meta-analysis. J Clin Endocrinol Metab, 2014, 99(10):3746–3755. doi: 10.1210/jc.2013-3795 Systematic review and meta-analysis*	The meta-analysis examined the time course of changes in bone mineral density (BMD) at the lumbar spine (LS) and total hip (TH) in postmenopausal women during treatment with denosumab, bisphosphonates, selective estrogen receptor modulators, parathyroid hormone (PTH) or calcitonin. A total of 142 RCTs, involving > 113 000 women, on prevention or treatment of postmenopausal osteoporosis provided data for the analysis. Overall, results indicated that 3 years of treatment with denosumab provides bigger changes in LS and TH BMD compared with 3 years of treatment with 10 mg/d oral alendronate, 5 mg/y iv zoledronic acid, 5 mg/d oral risedronate, 150 mg/mo oral ibandronate, 3 mg iv ibandronate every 3 months, 60 mg/d oral raloxifene, and 200 IU/d calcitonin. Although treatment with denosumab resulted in larger changes in TH BMD compared with PTH, treatment with PTH provided larger changes in LS BMD. The dose-response relationship for denosumab showed that the approved dosing regimen of 60 mg every 6 months results in maximal BMD changes.	**Section 6.4.10** The guideline recommendations do not detail dose regimens. **Section 6.5.6** No recommendation given, but one study reported that denosumab is safe and effective for up to five years. The new evidence does not change the existing advice.

Reference and study type*	Information likely to be relevant	Relevance to guideline
Lin et al. Alendronate versus raloxifene for postmenopausal women: a meta-analysis of seven head-to-head randomized controlled trials. International Journal of Endocrinology Volume 2014, Article ID 796510 Systematic review and meta-analysis*	This meta-analysis evaluated the efficacy and the safety of alendronate versus raloxifene for postmenopausal women. The analysis utilised data from seven RCTs, involving 4054 women, and found that alendronate was more effective than raloxifene in increasing bone mineral density (BMD). There were no statistical differences in reducing the risk of vertebral fractures (P = 0.45) or nonvertebral fractures (P = 0.87) for up to 2 years. Compared with raloxifene, alendronate reduced the risk of vasomotor (P = 0.006) but increased the risk of diarrhoea (P = 0.01). Subgroup analysis also showed that age did not affect the relative antifracture efficacy of alendronate and raloxifene. Compared with the daily treatment, weekly therapy for alendronate is associated with a reduction in upper GI disorders and an increase in bone mass. Adherence and side effects associated with each drugs should also be considered during management.	**Figure 3, and sections 6.4.1 and 6.4.13** Alendronic acid is recommended before raloxifene. No change required.
Lee, SH et al. Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis. Osteoporos Int (2014) 25:1131–1139 DOI 10.1007/s00198-013-2575-3 Systematic review and meta-analysis*	The review examined the use of bisphosphonates and risk of osteonecrosis of jaw or other sites among non-cancer patients. The review included 12 observational studies (including 2,652 cases and 1,571,997 controls) and found that bisphosphonates are associated with a substantial risk for osteonecrosis of jaw in cancer patients, with patients receiving bisphosphonates intravenously being at highest risk. Bisphosphonate use had a significantly increased risk of osteonecrosis of jaw or other sites [odds ratio (OR) 2.32; 95 % CI 1.38–3.91; I2=91 %]. Bisphosphonates were associated with higher risk on osteonecrosis of jaw (OR 2.57; 95 % CI 1.37–4.84; I 2=92.2 %) than osteonecrosis of other sites (OR 1.79; 95 % CI 0.71–4.47; I 2=83.3 %).	**Section 6.4.6** Guideline states: The number of identified cases was very small and the authors state that when used among patients at high risk of fracture, the balance of benefit to harm still favours bisphosphonates. There is insufficient evidence to conclude that, in the doses used to treat osteoporosis, oral or IV bisphosphonates lead to a significant risk of ONJ. [247] GPP: Patients starting bisphosphonates should be

Reference and study type*	Information likely to be relevant	Relevance to guideline
		advised to have a dental check up as soon as possible. Authors of the 2014 SR also conclude that the benefit of bisphosphonates outweighs the risk of ONJ. Potentially could strengthen the GPP or support a recommendation to highlight the risk (albeit small).
Frediani, B et al. Effect of clodronate treatment on risk of fracture: a systematic review and meta-analysis. Calcif Tissue Int (2014) 95:295–307 DOI 10.1007/s00223-014-9903-2 Systematic review and meta-analysis*	This review investigated the efficacy of clodronate in reducing the risk of fractures in patients with osteoporosis or tumour diseases. The review included 18 trials (13 studies involved patients with cancer diseases (breast cancer and multiple myeloma), 4 studies included patients with osteoporosis or low BMD and 1 study involved elderly women living in community) with the duration of treatment and follow up ranging from 3 months to 5 years. Results indicated that clodronate was associated with a reduced risk of new fractures compared with controls (OR = 0.572, 95% CI 0.465-0.704 for new vertebral fractures; OR = 0.668, 95% CI 0.494-0.905 for new non-vertebral fractures; and OR = 0.744, 95% CI 0.635-0.873 for new overall fractures in those articles where vertebral and non-vertebral new fractures were not considered separately). The review concluded that clodronate is effective in reducing the risk of vertebral, non-vertebral and overall fractures in patients with skeletal fragility.	Clodronate not included in guideline. Not relevant. Not used.
Feng, S et al. Efficacy and safety of odanacatib treatment for patients with osteoporosis: a	The review evaluated the efficacy and safety of odanacatib for treating osteoporosis. Data used for the meta-analysis were obtained from four trials. Results showed that 50 mg of odanacatib produced significantly greater increase in BMD and	Odanacatib is not included in the guideline. Not relevant. Company decided not to proceed

Reference and study type*	Information likely to be relevant	Relevance to guideline
meta-analysis. J Bone Miner Metab (2015) 33:448–454 DOI 10.1007/s00774-014-0609-3 Systematic review and meta-analysis*	lower fracture incidence compared with control. The mean difference (95 % CI) of lumbar spine BMD was 3.41 (1.57-5.24) at 12 months and 4.89 (2.72-7.05) at 24 months; mean difference (95 % CI) of femoral neck BMD was 1.90 (0.73-3.08) at 12 months and 3.85 (2.55-5.15) at 24 months; mean difference (95 % CI) of total hip BMD was 2.65 (1.20-4.09) at 12 months and 3.70 (1.76-5.64) at 24 months. Odanacatib was generally well tolerated. The risk ratio (95 % CI) of adverse events was 0.98 (0.91-1.07); risk ratio (95 % CI) of serious adverse events was 1.11 (0.72-1.72); risk ratio (95 % CI) of skin adverse events was 0.92 (0.63-1.35); and risk ratio (95 % CI) of fracture was 0.34 (0.16-0.70).	with marketing authorisation.
Ellis, AG et al. Bazedoxifene versus oral bisphosphonates for the prevention of nonvertebral fractures in postmenopausal women with osteoporosis at higher risk of fracture: a network meta-analysis. Value in health 17 (2014) 424 – 432 Systematic review and meta-analysis*	The review assessed the efficacy of bazedoxifene and oral bisphosphonates for the prevention of nonvertebral fractures in women with higher risk of postmenopausal osteoporosis (FRAX score ≥ 20%). The paper included nine bisphosphonate trials (alendronate, ibandronate, risedronate; n = 23,440 patients) with a similar placebo response as observed for the subgroup of high risk patients in the bazedoxifene trial. Results suggest that bazedoxifene appears to have an RRR of 0.43 (95% credible interval [CrI] -0.19 to 0.72) versus alendronate, 0.58 (95% CrI 0.05-0.81) versus ibandronate, and 0.39 (95% CrI -0.29 to 0.70) versus risedronate. Similar results were obtained from analyses that projected treatment effects with bisphosphonates to a population with a FRAX score of 20% or more. The review conclude that bazedoxifene is likely to have at least a comparable relative risk reduction of nonvertebral fractures as alendronate, ibandronate, and risedronate in women with higher risk of postmenopausal osteoporosis.	Bazedoxifene is not included in the guideline. This is a new drug which should be included (although not much used).

Reference and study type*	Information likely to be relevant	Relevance to guideline
Tadic I et al. New drugs for osteoporosis therapy: a review of the clinical trials phase 2 and 3. Scientific Journal of the Faculty of Medicine in Niš 2014;31(1):29-39 Systematic review*	The review assessed the efficacy of new drugs for osteoporosis currently in phase 2 and 3 clinical trials. Data from 10 papers was used to assess the efficacy of five drugs. Of these, only one paper reported data on fracture risk. The outcome measures were bone mineral density (BMD) and bone turnover markers (BTM). The highest increase of lumbar BMD from the baseline values (11.3%) was achieved after six months of subcutaneous application of 20 μg/day teriparatide. The lowest increase of BMD (2.1%) in the same region was recorded after six months of risedronate therapy (100 mg per os once monthly).	The focus of this review was on outcomes reported rather than comparison of efficacy of different therapies. No action required.
Song J et al. Single and combined use of human parathyroid hormone (PTH) (1-34) on areal bone mineral density (aBMD) in postmenopausal women with osteoporosis: evidence based on 9 RCTs. Med Sci Monit, 2014; 20: 2624-2632 Systematic review*	This review assessed the effect of teriparatide (TPTD) monotherapy and the additive effect of TPTD on antiresorptive (AR) agents in postmenopausal women with osteoporosis. The review included 9 RCTs and found that compared with placebo, TPTD alone could significantly improve BMD of femoral neck, total hip and lumbar spine. BMD outcomes of concomitant use of TPTD and AR agents were found to be site-dependent and varied depending on the AR agent used and the timing of AR therapy initiation	**Section 6.4.8** Recommendation: Teriparatide (parathyroid hormone 1-34) is recommended to prevent vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis and may be of particular value in patients at high risk of vertebral fracture. Not relevant, just BMD no fracture data. No action required.

KQ 5: For individuals prescribed pharmacological interventions, what is the optimal duration of treatment?

Reference and study type*	Information likely to be relevant	Impact on guideline
Adler et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for bone and mineral research. Journal of bone and mineral research, Vol. 31, No. 1, January 2016, pp 16–35 DOI: 10.1002/jbmr.2708 Report*	The report offers guidance on the duration of bisphosphonate therapy from a risk-benefit perspective. The guidance for long-term bisphosphonate use is based on evidence from two trials: 1) the Fracture Intervention Trial Long-term Extension (FLEX) trial where postmenopausal women received alendronate for 10 years and had fewer clinical vertebral fractures than those switched to placebo after 5 years; and 2) the HORIZON extension where women who received 6 annual infusions of zoledronic acid experienced fewer morphometric vertebral fractures compared with those switched to placebo after 3 years. The low hip T-score reported in the FLEX (between –2 and –2.5) and HORIZON extension (below –2.5) trials suggest a beneficial response to continued therapy. The Task Force suggests that: - reassessment of risk should be considered after 5 years of oral bisphosphonate or 3 years of intravenous bisphosphonate. - continuation of treatment for up to 10 years (oral) or 6 years (intravenous), with periodic evaluation, should be considered in women at high risk (older women, those with a low hip T-score or high fracture risk score, those with previous major osteoporotic fracture, or who fracture on therapy). The risk of atypical femoral fracture, but not osteonecrosis of the jaw, clearly increases with BP therapy duration, but such rare events are outweighed by vertebral fracture risk reduction in high-risk patients. - For women not at high fracture risk after 3 to 5 years of BP treatment, a drug holiday of 2 to 3 years can be considered.	The FLEX and HORIZON trials are both included in the evidence which has informed the recommendations in the guideline. No action required.

Reference and study type*	Information likely to be relevant	Impact on guideline
	The reports notes that the recommendations for long-term bisphosphonate use is based on limited evidence in mostly white postmenopausal women and should not replace the need for clinical judgment. Furthermore, the recommendations may be applicable and adapted to men and patients with glucocorticoid-induced osteoporosis. However, the reports notes that it is unlikely that future trials will provide data for formulating definitive recommendations.	

No evidence was identified that was specifically relevant to the following key questions:

- **KQ 3: Which diagnostic methods or tools best predict response to pharmacological treatment?**
- **KQ 6: What monitoring should be conducted in individuals taking pharmacological interventions?**
- **KQ 7: What interventions are effective in improving concordance with pharmacological interventions for fracture prevention?**
- **KQ 8: What exercise interventions are effective in reducing the risk of fracture or improving BMD levels?**
- **KQ 9: What dietary interventions are effective in reducing the risk of fracture or improving BMD levels?**

KQ 10: What is the clinical and cost effectiveness of integrated models of care (which include assessment, identification, treatment and follow up) compared with stand-alone elements for the primary and secondary prevention of fragility fracture?

Reference and study type*	Information likely to be relevant	Impact on guideline
Jensen AL et al. Effectiveness and characteristics of multifaceted osteoporosis group education—a systematic review. Osteoporos Int (2014) 25:1209–1224 Systematic review*	The review examined the characteristics and effectiveness of osteoporosis multifaceted group education and found that the educational programmes may have benefits in a number of essential factors for the prevention, treatment and management of osteoporosis. The review included seven studies including osteoporosis patients with or without fractures. Although programmes varied in their area of focus, they all comprised of the following themes: exercise, medication and diet, and knowledge of osteoporosis. The findings suggest that multifaceted osteoporosis group education can help increase patients' knowledge of osteoporosis and their psychosocial functioning, physical activity and health-related quality of life. There was also the potential to increase adherence to treatments (pharmacological and non-pharmacological).	**Section 8.2** No recommendation. Conclusion was that multifactorial approaches involving education… appear to be moderately successful in promoting initiation of osteoporosis therapies. Jensen et al also concluded "Multifaceted group education may have a positive impact on the patients' ability to engage in preventing and managing osteoporosis. Further research directed towards the complexity of multifaceted group education is needed." No action required.

KQ 11: In individuals with vertebral fracture, which interventions reduce pain, reduce deformity and improve outcome?

Reference and study type*	Information likely to be relevant	Impact on guideline
Buchbinder, R et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. Cochrane Database of Systematic Reviews. 2015. Systematic review*	The review examined the benefits and harms of vertebroplasty for treatment of osteoporotic vertebral fractures. The review identified 11 RCTs and one quasi-RCT, of which two trials compared vertebroplasty with placebo (209 participants), six compared vertebroplasty with usual care (566 participants) and four compared vertebroplasty with kyphoplasty (545 participants). The majority of participants were female and duration of the trials varied from 1 week to >6 months. The placebo-controlled trials were considered to have low overall risk of bias while the other trials were deemed to have high risk of bias. The review concluded that the evidence (moderate quality) does not support a role for vertebroplasty for treating osteoporotic vertebral fractures in routine practice. There was no demonstrable clinically important benefits compared with a sham procedure. In addition, subgroup analyses showed that results did not differ according to duration of pain (6 weeks vs > 6 weeks). Sensitivity analyses indicated that open trials comparing vertebroplasty with usual care are likely to have overestimated any benefit of vertebroplasty. The trials also reported a number of serious adverse events after vertebroplasty. However, it was difficult to determine whether or not vertebroplasty results in an increased risk of new symptomatic vertebral fractures and/or other serious adverse events due to the small number of events.	**Section 7.6.1** No recommendation made. No action required.
Xiao, H et al. Comparing complications of vertebroplasty and kyphoplasty for treating osteoporotic vertebral	The review assessed complications of percutaneous vertebroplasty (PVP) and balloon kyphoplasty (BKP) for the treatment of osteoporotic vertebral compression fractures (OVCFs). Based on data from 19 studies including 1,787 patients (887 received PVP and 900 received BKP), the review concluded that both procedures have equal risk of subsequent spinal fractures. Meta-analysis did not identify any significant difference between the two procedures for	**Section 7.6.1** No recommendation made. This would not change the advice given.

Reference and study type*	Information likely to be relevant	Impact on guideline
compression fractures: a meta-analysis of the randomized and non-randomized controlled studies. Eur J Orthop Surg Traumatol (2015) 25 (Suppl 1):S77–S85 Systematic review and meta-analysis*	non-adjacent fractures (p = 0.37) and adjacent fractures (p = 0.29). As regards to cement extravasations, there was no significant difference between the two interventions if disc spaces were considered, while PVP group showed a significantly higher cement leakage rate than the BKP group (total: p<0.01; paravertebral: p<0.01) when the total extravasations and paravertebral extravasations were considered.	No action required.
Tian, J et al. The clinical efficacy of vertebroplasty on osteoporotic vertebral compression fracture: a meta-analysis. International Journal of Surgery 12 (2014) 1249-1253 Systematic review and meta-analysis*	The review assessed the clinical efficacy of vertebroplasty for the treatment of osteoporotic vertebral compression fracture. The meta-analysis utilised data from 5 studies and found statistically significant improvements in pain relief in favour of vertebroplasty compared with traditional treatment and comparable incidence of adjacent vertebral fracture between the patients treated by VP and traditional treatment. The Visual Analogue Scale (VAS) score of patients treated with VP was significantly lower than that treated with traditional treatment at each time point (one week: WMD = −2.55, 95% CI, −3.08 to −2.02, P < 0.0001; 12 weeks: WMD = −0.90, 95% CI, −1.22 to −0.57, P < 0.0001; 24 weeks: WMD = −1.75, 95% CI, −2.30 to −1.19, P < 0.0001; 48 weeks: WMD = −1.75, 95% CI, −2.30 to −1.19, P < 0.001). The overall estimate (OR = 2.06, 95% CI: 0.26 to 16.29, P = 0.50) showed that there was no statistically significant difference between vertebroplasty and traditional treatment, for incidence of adjacent vertebral fracture.	**Section 7.6.1** No recommendation made. No action required.

Reference and study type*	Information likely to be relevant	Impact on guideline
Stevenson M et al. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. Health Technol Assess 2014;18(17). Health technology assessment*	This health technology assessment evaluated the clinical and cost effectiveness of percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (BKP) in reducing pain and disability in people with osteoporotic vertebral compression fractures (VCFs) in England and Wales. Nine RCTs of variable quality were included in the review of clinical effectiveness. Overall, results showed that PVP and BKP perform significantly better in unblinded trials than optimal pain management in terms of improving quality of life and reducing pain and disability, for people with painful osteoporotic VCFs refractory to analgesic treatment. There is still no strong evidence to suggest that either procedure performs better than operative placebo with local anaesthesia (OPLA). Findings from the cost-effectiveness analyses suggest that BKP, PVP and OPLA appear most cost-effective depending on the assumptions made regarding utility, OPLA costs, hospitalisation costs and mortality effects.	**Section 7.6.1** No recommendation made. No action required.
Song D et al. The incidence of secondary vertebral fracture of vertebral augmentation techniques versus conservative treatment for painful osteoporotic vertebral fractures: a systematic review and meta-analysis.	The review assessed the effects of vertebral augmentation techniques and conservative treatment for managing osteoporotic vertebral compression fractures on the incidence of secondary vertebral fractures. The review identified 13 articles and pooled results showed no statistically significant differences in the incidence of secondary vertebral fractures between patients treated with vertebral augmentation techniques and conservative treatment. Subgroup analysis (comparing different study designs, symptoms duration, follow-up period, racial background and techniques used) found no significant differences in the incidence of secondary fractures ($P > 0.05$).	**Section 7.6.1** No recommendation made. No action required.

Reference and study type*	Information likely to be relevant	Impact on guideline
Acta Radiologica (2015) Vol 56, Issue 8, pp. 970 - 979 Systematic review and meta-analysis*		
Huang, Z et al. Is unilateral kyphoplasty as effective and safe as bilateral kyphoplasties for osteoporotic vertebral compression fractures? A meta-analysis. Clin Orthop Relat Res (2014) 472:2833–2842 Systematic review and meta-analysis*	The review assessed whether unilateral kyphoplasty is as effective and safe as bilateral kyphoplasties for osteoporotic vertebral compression fractures. The review included five studies involving 253 patients and found that both approaches (unilateral and bilateral percutaneous kyphoplasties) appear to be safe and effective for treating osteoporotic vertebral compression fractures. Based on the VAS and Oswestry Disability Index, there were no clinically important differences between them ($p = 0.41$, $p = 0.60$ for VAS; $p = 0.10$, $p = 0.36$ for Oswestry Disability Index). There was also no difference in complications (cement leakage and adjacent vertebral fractures) associated with the two approaches ($p = 0.43$ and $p = 0.95$). The kyphosis angle reduction and anterior vertebral height restoration found no difference ($p = 0.34$ and $p = 0.46$). The evidence also suggested that unilateral percutaneous kyphoplasty was associated with less operation time (mean difference, -24.98; $p<0.0001$) and less cost.	Comparison between unilateral and bilateral kyphoplasties is not included in the guideline. No action required.

Evidence that cut across several KQs

Reference and study type*	Information likely to be relevant	Impact on guideline
American College of Rheumatology. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis & Rheumatology Vol. 69, No. 8, August 2017, pp 1521–1537 Clinical guideline*	This guideline offers recommendations for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP). The guideline notes that most recommendations are conditional (uncertain balance between benefits and harms) due to limited evidence and advises the recommendations should not be used to deny or limit access to treatment. **Recommendations** **<u>Recommendations for initial treatment for prevention of GIOP in adults (women not of child-bearing potential and men) beginning long-term GC treatment*</u>** **All adults taking prednisone at a dose of ≥2.5 mg/day for ≥3 months** • **Optimize calcium intake** (1,000–1,200 mg/day)* **and vitamin D intake** (600–800 IU/day) **and lifestyle modifications** (balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) **over no treatment or over any of these treatments alone**. • **Conditional recommendation** because of indirect evidence on the impact of lifestyle modifications on fracture risk, low-quality evidence on the impact of calcium and vitamin D on fractures in GC users, and indirect evidence on the benefit of calcium and vitamin D on fracture risk in the general OP population **Adults age ≥40 years at low risk of fracture** • **Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, denosumab, or raloxifene**.	Section 7.5: Glucocorticoid-induced osteoporosis Recommendations: Alendronic acid may be considered to prevent vertebral fractures in men and women on prednisolone doses of 7.5 mg daily or greater (or an equivalent dose of glucocorticoids) for three months or more. Risedronate should be considered to prevent vertebral fracture in men and women on prednisolone doses of 7.5 mg daily or greater (or an equivalent dose of glucocorticoids) for three months or more. Zoledronic acid should be considered to prevent vertebral fracture in men and women on prednisolone doses of 7.5 mg daily or greater (or an equivalent dose of glucocorticoids) for three months or more. The treatment should be considered in patients who are intolerant of oral bisphosphonates and those in whom adherence to oral therapy may be difficult. There is no new evidence in this area. Unlikely to change existing recommendations.

Reference and study type*	Information likely to be relevant	Impact on guideline
	• **Conditional recommendation** for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments in this low-risk group, costs, and potential harms • **Strong recommendation** for calcium and vitamin D over IV bisphosphonates and raloxifene because of low-quality evidence on additional antifracture benefit in this low-risk group and their potential harms **Adults age ≥40 years at moderate risk of major fracture** • **Treat with an oral bisphosphonate over calcium and vitamin D alone.** • **Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.** • Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. • Other therapies if oral bisphosphonates are not appropriate, in order of preference: o IV bisphosphonates ▪ Higher risk profile for IV infusion over oral bisphosphonate therapy o Teriparatide ▪ Cost and burden of therapy with daily injections o Denosumab ▪ Lack of safety data in people treated with immunosuppressive agents o Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate) ▪ Lack of adequate data on benefits (impact on risk of	

Reference and study type*	Information likely to be relevant	Impact on guideline
	vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality) • **Conditional recommendations** because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with moderate fracture risk **Adults age ≥40 years at high risk of fracture** • **Treat with an oral bisphosphonate over calcium and vitamin D alone.** • **Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.** • Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. • Other therapies if oral bisphosphonates are not appropriate, in order of preference: o IV bisphosphonates ▪ Higher risk profile for IV infusion over oral bisphosphonate therapy o Teriparatide ▪ Cost and burden of therapy with daily injections o Denosumab ▪ Lack of safety data in people treated with immunosuppressive agents o Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate) ▪ Lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality) • **Strong recommendation** for oral bisphosphonates over calcium and vitamin D alone because of the strength of the indirect	

Reference and study type*	Information likely to be relevant	Impact on guideline
	evidence of antifracture efficacy and low harms • All other recommendations **conditional** because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with high fracture risk **Adults age <40 years at low risk of fracture** • **Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, or denosumab.** • **Conditional recommendation** for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments, costs, and potential harms • **Strong recommendation** for calcium and vitamin D over IV bisphosphonates because of low-quality evidence for additional antifracture benefit in this low-risk group and potential harms **Adults age <40 years at moderate-to-high risk of fracture** • **Treat with an oral bisphosphonate over calcium and vitamin D alone.** • **Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.** • Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. • Other therapies if oral bisphosphonates are not appropriate, in order of preference: o IV bisphosphonates ▪ Higher risk profile for IV infusion over oral bisphosphonate therapy o Teriparatide	

Reference and study type*	Information likely to be relevant	Impact on guideline
	▪ Cost and burden of therapy with daily injections o Denosumab ▪ Lack of safety data in people treated with immunosuppressive agents • **Conditional recommendations** because of low- to very low-quality evidence on absolute fracture risk and indirect and low-quality evidence comparing relative harms and benefits of alternative treatments in this age group **<u>Recommendations for initial treatment for prevention of GIOP in special populations of patients beginning long-term GC treatment</u>*** **Women of childbearing potential at moderate-to-high risk of fracture who do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active** • **Treat with an oral bisphosphonate over calcium and vitamin D alone, teriparatide, IV bisphosphonates, or denosumab.** • Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. • Other therapies if oral bisphosphonates are not appropriate, in order of preference: o Teriparatide ▪ Safety, cost, and burden of therapy with daily injections Consider the following therapies only for high-risk patients because of lack of safety data on use of these agents during pregnancy: o IV bisphosphonates ▪ Potential fetal risks of IV infusion during pregnancy o Denosumab	

Reference and study type*	Information likely to be relevant	Impact on guideline
	▪ Potential fetal risks during pregnancy • **Conditional recommendations** because of indirect and very low-quality evidence on benefits and harms of these treatments to the fetus during pregnancy **Adults age ≥30 years receiving very high-dose GCs (initial dose of prednisone ≥30 mg/day and cumulative dose >5 gm in 1 year)** • **Treat with an oral bisphosphonate over calcium and vitamin D alone.** • **Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.** • Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of additional antifracture benefits from other OP medications. • If bisphosphonate treatment is not appropriate, alternative treatments are listed by age (≥40 years and ≥40 years). • **Conditional recommendations** because of low-quality evidence on absolute fracture risk and harms in this population **Adults with organ transplant, glomerular filtration rate ≥30 ml/minute, and no evidence of metabolic bone disease who continue treatment with GCs** • **Treat according to the age-related guidelines for adults without transplants, with these additional recommendations:** o An evaluation by an expert in metabolic bone disease is recommended for all patients with a renal transplant. o Recommendation against treatment with denosumab due to lack of adequate safety data on infections in adults treated with multiple immunosuppressive agents. • **Conditional recommendations** because of low-quality evidence on antifracture efficacy in transplant recipients and on relative	

Reference and study type*	Information likely to be relevant	Impact on guideline
	benefits and harms of the alternative treatments in this population **Children ages 4–17 years treated with GCs for ≥3 months** • **Optimize calcium intake (1,000 mg/day) and vitamin D intake (600 IU/day) and lifestyle modifications over not optimizing calcium and vitamin D intake and lifestyle modifications.** • **Conditional recommendation** because of lack of antifracture efficacy of calcium and vitamin D in children but limited harms **Children ages 4–17 years with an osteoporotic fracture who are continuing treatment with GCs at a dose of ≥0.1 mg/kg/day for ≥3 months** • **Treat with an oral bisphosphonate (IV bisphosphonate if oral treatment contraindicated) plus calcium and vitamin D over treatment with calcium and vitamin D alone.** • **Conditional recommendation** because of very low-quality antifracture data in children but moderate-quality evidence of low harms of oral bisphosphonates in children and less potential harm of oral over IV bisphosphonates **<u>Recommendations for follow-up treatment for prevention of GIOP*</u>** **Adults age ≥40 years continuing GC treatment who have had a fracture that occurred after ≥18 months of treatment with an oral bisphosphonate or who have had a significant loss of bone mineral density (≥10%/year)** • **Treat with another class of OP medication (teriparatide or denosumab; or, consider IV bisphosphonate if treatment failure is judged to be due to poor absorption or poor medication adherence) with calcium and vitamin D over**	

Reference and study type*	Information likely to be relevant	Impact on guideline
	calcium and vitamin D alone or over calcium and vitamin D and continued oral bisphosphonate. • **Conditional recommendation** because of very low-quality evidence comparing benefits and harms of the compared treatment options in this clinical situation **Adults age ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture** • **Continue active treatment (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate [if concern with regard to adherence or absorption] or switch to an OP treatment in another class) over calcium and vitamin D alone.** • **Conditional recommendation** because of very low-quality data on benefits and harms in GC-treated patients, but moderate-quality data in the general OP literature on benefits and harms of continuing treatment with oral bisphosphonates past 5 years for people at high risk of fracture **Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at low risk of fracture** • **Discontinue the OP medication but continue calcium and vitamin D over continuing the OP medication.** • **Conditional recommendation** made by expert consensus; evidence informing it too indirect for the population and very low-quality **Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are**	

Reference and study type*	Information likely to be relevant	Impact on guideline
	assessed to be at moderate-to-high risk of fracture • **Complete the treatment with the OP medication over discontinuing the OP medication.** • **Strong recommendation** for high-risk patients based on expert consensus that patients who are at high risk should continue an OP treatment in addition to calcium and vitamin D • **Conditional recommendation** for moderate-risk patients because of lower fracture risk compared to potential harms	
Kidney Disease: Improving Global Outcomes. Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD), 2017 Clinical guideline*	**Recommendations** **Diagnosis of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD): Biochemical Abnormalities** • The Work Group recommends monitoring serum levels of calcium, phosphorus, parathyroid hormone (PTH), and alkaline phosphatase activity beginning in chronic kidney disease (CKD) G3a (**1C**). In children, the Work Group suggests such monitoring beginning in CKD G2 (**2D**). • In patients with CKD G3a–G5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (**Not Graded**). Reasonable monitoring intervals would be: o In CKD G3a–G3b: for serum calcium and phosphate, every 6 to 12 months; and for PTH, based on baseline level and CKD progression. o In CKD G 4: for serum calcium and phosphate, every 3 to 6 months; and for PTH, every 6 to 12 months. o In CKD G5, including 5D: for serum calcium and phosphate, every 1 to 3 months; and for PTH, every 3 to 6 months. o In CKD G4–G5D: for alkaline phosphatase activity, every 12	**Section 3.4.11** People over the age of 50 with moderate to severe chronic kidney disease (eGFR <60 ml/min/1.73m^2) may be considered for fracture-risk assessment, particularly in the presence of other risk factors. GPP: The assessment and management of osteoporosis in patients with CKD who have an eGFR min/1.73 m^2 is complex and should be undertaken by specialists with experience in the area. The new evidence recommends treatment in line with the general osteoporosis population. The rest is outside the remit of SIGN 142.

Reference and study type*	Information likely to be relevant	Impact on guideline
	months, or more frequently in the presence of elevated PTH (see "Diagnosis of CKD–MBD: Bone," below). In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side effects (**Not Graded**). • In patients with CKD G3a–G5D, the Work Group suggests that 25-hydroxyvitamin D [25(OH)D] (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (**2C**). The Work Group suggests that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (**2C**). • In patients with CKD G3a–G5D, the Work Group recommends that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD–MBD assessments (**1C**). • In patients with CKD G3a–G5D, the Work Group suggests that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium–phosphorus product (Ca x P) (**2D**). • In reports of laboratory tests for patients with CKD G3a–G5D, the Work Group recommends that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), or handling specifications to facilitate the appropriate interpretation of biochemistry data (**1B**).	

Reference and study type*	Information likely to be relevant	Impact on guideline
	Diagnosis of CKD–MBD: Bone • In patients with CKD G3a–G5D with evidence of CKD–MBD and/or risk factors for osteoporosis, the Work Group suggests bone mineral density (BMD) testing to assess fracture risk if results will impact treatment decisions (**2B**). • In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (**Not Graded**). • In patients with CKD G3a–G5D, the Work Group suggests that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (**2B**). • In patients with CKD G3a–G5D, the Work Group suggests not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (**2C**). • The Work Group recommends that infants with CKD G2–G5D should have their length measured at least quarterly, while children with CKD G2–G5D should be assessed for linear growth at least annually (**1B**). • Diagnosis of CKD–MBD: Vascular Calcification • In patients with CKD G3a–G5D, the Work Group suggests that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (**2C**). • The Work Group suggests that patients with CKD G3a–G5D with known vascular or valvular calcification be considered at highest	

Reference and study type*	Information likely to be relevant	Impact on guideline
	cardiovascular risk (**2A**). It is reasonable to use this information to guide the management of CKD–MBD (**Not Graded**). **Treatment of CKD–MBD Targeted at Lowering High Serum Phosphate and Maintaining Serum Calcium** • In patients with CKD G3a–G5D, treatments of CKD–MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (**Not Graded**). • In patients with CKD G3a–G5D, the Work Group suggests lowering elevated phosphate levels toward the normal range (**2C**). • In adult patients with CKD G3a–G5D, the Work Group suggests avoiding hypercalcemia (**2C**). In children with CKD G3a–G5D, the Work Group suggests maintaining serum calcium in the age-appropriate normal range (**2C**). • In patients with CKD G5D, the Work Group suggests using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (**2C**). • In patients with CKD G3a–G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (**Not Graded**). • In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, the Work Group suggests restricting the dose of calcium-based phosphate binders (**2B**). In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (**Not Graded**). • In patients with CKD G3a–G5D, the Work Group recommends avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (**1C**). • In patients with CKD G3a–G5D, the Work Group suggests	

Reference and study type*	Information likely to be relevant	Impact on guideline
	limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (**2D**). It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations (**Not Graded**). • In patients with CKD G5D, the Work Group suggests increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (**2C**). **Treatment of Abnormal PTH Levels in CKD–MBD** • In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, the Work Group suggests that patients with levels of intact PTH (iPTH) progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (**2C**). • In adult patients with CKD G3a–G5 not on dialysis, the Work group suggests that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (Not Graded). In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (**Not Graded**). • In patients with CKD G5D, the Work Group suggests maintaining iPTH levels in the range of approximately 2 to 9 times the upper normal limit for the assay (**2C**). The Work Group suggests that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of	

Reference and study type*	Information likely to be relevant	Impact on guideline
	this range (**2C**). • In patients with CKD G5D requiring PTH-lowering therapy, the Work Group suggests calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (**2B**). • In patients with CKD G3a–G5D with severe hyperparathyroidism (HPT) who fail to respond to medical or pharmacological therapy, the Work Group suggests parathyroidectomy (**2B**). **Treatment of Bone with Bisphosphonates, Other Osteoporosis Medications, and Growth Hormone** • In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization (WHO) criteria, the Work Group recommends management as for the general population (**1A**). • In patients with CKD G3a–G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by WHO criteria, the Work Group suggests treatment as for the general population (**2B**). • In patients with CKD G3a–G5D with biochemical abnormalities of CKD–MBD and low BMD and/or fragility fractures, the Work Group suggests that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (**2D**). • In children and adolescents with CKD G2–G5D and related height deficits, the Work Group recommends treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD–MBD (**1A**). **Evaluation and Treatment of Kidney Transplant Bone Disease**	

Reference and study type*	Information likely to be relevant	Impact on guideline
	• In patients in the immediate post–kidney-transplant period, the Work Group recommends measuring serum calcium and phosphate at least weekly, until stable (**1B**). • In patients after the immediate post–kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (**Not Graded**). Reasonable monitoring intervals would be: o In CKD G1T–G3bT, for serum calcium and phosphate, every 6 to 12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression. o In CKD G4T, for serum calcium and phosphate, every 3 to 6 months; and for PTH, every 6 to 12 months. o In CKD G5T, for serum calcium and phosphate, every 1 to 3 months; and for PTH, every 3 to 6 months. o In CKD G3aT–G5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see "Diagnosis of CKD–MBD: Bone," above). In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side effects (**Not Graded**). It is reasonable to manage these abnormalities as for patients with CKD G3a–G5 (**Not Graded**) (see "Treatment of CKD–MBD Targeted at Lowering High Serum Phosphate and Maintaining Serum Calcium" and "Treatment of Abnormal PTH Levels in CKD–MBD," above). • In patients with CKD G1T–G5T, the Work Group suggests that 25(OH)D (calcidiol) levels might be measured, and repeated	

Reference and study type*	Information likely to be relevant	Impact on guideline
	testing determined by baseline values and interventions (**2C**). • In patients with CKD G1T–G5T, the Work Group suggests that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (**2C**). • In patients with CKD G1T–G5T with risk factors for osteoporosis, the Work Group suggests that BMD testing be used to assess fracture risk if results will alter therapy (**2C**). • In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m2 and low BMD, the Work Group suggests that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (**2D**). o The Work Group suggests that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (**2C**). o It is reasonable to consider a bone biopsy to guide treatment (**Not Graded**). There are insufficient data to guide treatment after the first 12 months. • In patients with CKD G4–G5T with known low BMD, the Work Group suggests management as for patients with CKD G4–G5 not on dialysis, as detailed in "Treatment of CKD–MBD Targeted at Lowering High Serum Phosphorus and Maintaining Serum Calcium" and "Treatment of Abnormal PTH Levels in CKD–MBD," above (**2C**).	

Reference and study type*	Information likely to be relevant	Impact on guideline
Dynamed Plus. Bisphosphonates for treatment and prevention of osteoporosis. 2017 Evidence-based summary*	**Alendronate efficacy for treatment of postmenopausal osteoporosis** • **older age and lower hip bone mineral density at time of discontinuation of alendronate associated with increased risk of clinical fracture in postmenopausal women during subsequent 5 years following 4-5 years of alendronate therapy (level 2 [mid-level] evidence)** o based on post hoc analysis of the FLEX trial including 437 postmenopausal women aged 61-86 years previously treated with alendronate for 4-5 years discontinued therapy and followed for additional 5 years. Of these, 22% had ≥ 1 symptomatic fracture o compared with other 2 tertiles, there was an increased risk of fracture for lowest tertile for bone mineral density for ▪ femoral neck (adjusted hazard ratio [HR] 2.17, 95% CI 1.38-3.41) ▪ total hip (adjusted HR 1.87, 95% CI 1.2-2.92) o older age was associated with increased risk of fracture (HR per 5-year increase in age 1.54, 95% CI 1.26-1.85) • **addition of alendronate to cholecalciferol (vitamin D) may increase bone marrow density without affecting serum or urinary calcium levels in postmenopausal women with osteoporosis and normocalcemic primary hyperparathyroidism (level 3 [lacking direct] evidence)** o based on a small randomised trial of 30 postmenopausal women with osteoporosis and normocalcemic hyperparathyroidism randomised to alendronate 70 mg plus cholecalciferol (vitamin D) 2,800 units orally/week (tablet) vs. same dose of cholecalciferol alone (11 drops)	**Section 6.5.2** Recommendation: Alendronic acid may be continued for up to 10 years in postmenopausal women with osteoporosis, especially those that are at high risk of vertebral fracture. No change required. Based on one small RCT – insufficient to support a SIGN recommendation.

Reference and study type*	Information likely to be relevant	Impact on guideline
	o patients were followed for 1 year post treatment and ▪ bone marrow density (BMD) measured at 1 year ▪ bone turnover markers (BTM) measured at 3 and 6 months o compared to baseline, women treated with alendronate/cholecalciferol had ▪ increased BMD at the lumbar, femoral neck and hip level at 1 year ($p = 0.001$) ▪ decreased BTM at 3 and 6 months ($p < 0.001$) o there were no significant differences in ▪ BMD or BTM in patients treated with cholecalciferol alone compared to baseline ▪ serum calcium, parathyroid hormone levels and urinary calcium levels between groups or compared to baseline o no cases of hypercalcemia or hypercalciuria were reported **Ibandronate efficacy for treatment of postmenopausal osteoporosis** • **ibandronate for 5 years has been reported to decrease clinical fracture rate in postmenopausal women with osteoporosis (level 3 [lacking direct] evidence)** o based on pooled analysis of long-term extension studies from 3 randomised trials comparing clinical fracture rates with ibandronate vs. placebo in postmenopausal women with osteoporosis ▪ ibandronate rates from pooled analysis of MOBILE and DIVA trials ▪ placebo rates from BONE trial o ibandronate treatment included ibandronate 150 mg/month	Recommendations Oral ibandronic acid (150 mg monthly) may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis. Intravenous ibandronic acid (3 mg every three months) may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis who are intolerant of oral therapy or those in whom adherence to oral therapy may be difficult.

Reference and study type*	Information likely to be relevant	Impact on guideline
	orally, ibandronate 2 mg IV every 2 months or ibandronate 3 mg IV quarterly o in adjusted analysis with indirect comparisons, continuous ibandronate treatment for 5 years with annual cumulative exposure ≥ 10.8 mg was associated with increased ▪ time to any clinical fracture ($p < 0.001$) ▪ increase in time to nonvertebral fracture ($p = 0.036$) ▪ increased time to clinical vertebral fracture ($p = 0.003$) **Zoledronic acid efficacy for treatment of postmenopausal osteoporosis** • **single dose of zoledronic acid may improve hip and spine bone mineral density (level 3 [lacking direct] evidence) but may not reduce fractures in frail elderly women with osteoporosis (level 2 [mid-level] evidence)** o based on a randomised trial of 181 women ≥ 65 years old (mean age 85 years) with osteoporosis (including women with cognitive impairment, immobility, and multimorbidity) living in nursing home and assisted living facilities randomised to single-dose zoledronic acid 5 mg vs. placebo intravenously and followed for 24 monthsn (76% completed). All women received daily calcium and vitamin D supplementation. The study not powered to detect differences in clinical outcomes o comparing zoledronic acid vs. placebo ▪ mean change in bone mineral density (primary	Recommendations: Zoledronic acid is recommended to prevent vertebral, non-vertebral and hip fractures in postmenopausal women with pre-existing vertebral fractures or DXA-proven osteoporosis. It should be considered in those who are intolerant of oral therapy and those in whom adherence with oral therapy may be difficult. Zoledronic acid may be considered to prevent clinical fractures and reduce mortality in selected postmenopausal women who have suffered a hip fracture. It should be considered in those who are intolerant of oral therapy and those in whom adherence with oral therapy may be difficult.

Reference and study type*	Information likely to be relevant	Impact on guideline
	outcome) of ▪ hip +2.6% vs. -1.5% (p < 0.001) ▪ spine +4.5% vs. +0.7% (p < 0.001) ▪ fracture rate 20% vs. 16% (not significant) ▪ mortality rate 16% vs. 13% (not significant) ▪ proportion of single fallers 28% vs. 24% (not significant) ▪ proportion of multiple fallers 49% vs. 35% (not significant when adjusted for baseline frailty) **Risedronate efficacy for men with osteoporosis** • **inconsistent evidence for effect of risedronate on risk of vertebral fracture in men with osteoporosis** o based on a systematic review of 22 trials evaluating treatment to reduce fractures in 4,868 men with osteoporosis or low bone mineral density (T-score ≤ -1). Two trials evaluated addition of risedronate to calcium plus vitamin D (duration 2 years). Both trials had unclear allocation concealment and no or unclear blinding o risedronate was associated with significantly decreased risk of vertebral fracture in 1 trial with 316 patients but no significant difference in risk with wide confidence including possibility of benefit or harm in 1 trial with 284 patients **Drug class efficacy for steroid-induced osteoporosis** • **bisphosphonates may reduce risk of vertebral fracture in adults taking systemic corticosteroids for inflammatory disorders (level 2 [mid-level] evidence)** o based on a systematic review of 27 randomised trials	These recommendations are based on a larger evidence base than the one RCT cited by Dynamed. There may be a need for a minor change around harms to include a statement that patients should be informed of the risks. Section 7.3.2 The evidence base for risedronate in men is described but no recommendation given as it is not accepted for use in men with osteoporosis at increased risk of fracture within NHSScotland by the Scottish Medicines Consortium. No change required. Section 7.5: Glucocorticoid-induced osteoporosis Recommendations:

Reference and study type*	Information likely to be relevant	Impact on guideline
	comparing bisphosphonates vs. placebo or no treatment in 3,075 adults taking steroids (mean corticosteroid dose ≥ 5 mg per day) for inflammatory disorders ▪ 13 trials evaluated prevention of glucocorticoid-induced osteoporosis and 14 trials evaluated treatment of glucocorticoid-induced osteoporosis ▪ most trials assessed addition of bisphosphonate to calcium, vitamin D or both o bisphosphonates included alendronate (9 trials), cyclic etidronate (8 trials), pamidronate (3 trials), clodronate (3 trials), risedronate (2 trials) and ibandronate (2 trials). The duration of the trial was typically ≥ 12 months o bisphosphonates were associated with ▪ reduced risk of radiographic vertebral fracture at 12-24 months in analysis of 12 trials with 1,343 patients, but confidence interval includes differences that may not be clinically important ▪ risk ratio 0.57 (95% CI 0.35-0.91) ▪ NNT 20-139 with radiographic vertebral fracture in 8% of control group ▪ symptomatic and asymptomatic vertebral fractures combined for analysis ▪ increase in bone mineral density at lumbar spine at 18-24 months (mean difference [MD] 5.49%, 95% CI 3.47%-7.51%) in analysis of 9 trials with 802 patients ▪ increase in bone mineral density at femoral neck at 18-24 months (MD 3.28%, 95% CI 1.7%-4.87%) in analysis of 9 trials with 802 patients, results limited by significant heterogeneity o there were no significant differences in ▪ radiographic nonvertebral fractures at 12-24	Alendronic acid may be considered to prevent vertebral fractures in men and women on prednisolone doses of 7.5 mg daily or greater (or an equivalent dose of glucocorticoids) for three months or more. Risedronate should be considered to prevent vertebral fracture in men and women on prednisolone doses of 7.5 mg daily or greater (or an equivalent dose of glucocorticoids) for three months or more. Zoledronic acid should be considered to prevent vertebral fracture in men and women on prednisolone doses of 7.5 mg daily or greater (or an equivalent dose of glucocorticoids) for three months or more. The treatment should be considered in patients who are intolerant of oral bisphosphonates and those in whom adherence to oral therapy may be difficult. No change to SIGN 142 required.

Reference and study type*	Information likely to be relevant	Impact on guideline
	months in analysis of 9 trials with 1,245 patients ▪ serious adverse events at 12-24 months in analysis of 15 trials with 1,703 patients **Alendronate efficacy for steroid-induced osteoporosis** • **alendronate may reduce risk of hip fracture in older patients treated with prednisolone ≥ 5mg/day for ≥ 3 months (level 2 [mid-level] evidence)** o based on a retrospective cohort study of 7,878 patients (≥ 65 years old) registered in Swedish Senior Alert database between 2008 and 2014 and treated with either prednisolone ≥ 5 mg/day orally for ≥ 3 months plus alendronate or prednisolone alone and assessed for rates of incident fracture. Propensity score for likelihood of alendronate use was calculated for each patient based on anthropometric variables, clinical risk factors and comorbidities o all 1,802 patients (mean age 80 years, 70% female) using prednisolone plus alendronate were propensity score-matched to 1,802 patient using prednisolone alone ▪ median follow-up in propensity-score matched cohort 1.3 years ▪ median time from start of prednisolone to start of alendronate therapy 3.9 months ▪ median duration of prednisolone therapy 4.6 years and median alendronate therapy 2.9 years prior to baseline o comparing alendronate use vs. no use in propensity score-matched cohort, incidence rates per 1,000 person-years ▪ hip fracture 9.5 vs. 27.2 (adjusted hazard ratio [HR] 0.35, 95% CI 0.22-0.54)	Guideline says 7.5 mg/day. Dynamed study is from 2017. This could be considered for update.

Reference and study type*	Information likely to be relevant	Impact on guideline
	▪ nonvertebral fracture 37.2 vs. 66 (adjusted HR 0.55, 95% CI 0.43-0.71) ▪ hip, wrist, shoulder, or clinical vertebral fracture 21.2 vs. 40.1 (adjusted HR 0.53, 95% CI 0.38-0.73) ▪ any fracture 43.4 vs. 73.3 (adjusted HR 0.58, 95% CI 0.46-0.73) o there were no significant differences in mild upper gastrointestinal tract symptoms (dyspepsia, acid reflux, and esophagitis) or peptic ulcers **Cystic fibrosis (CF)** • **bisphosphonates appear to increase bone mineral density (level 3 [lacking direct] evidence) but may increase bone pain and may not reduce fractures (level 2 [mid-level] evidence) in adults with CF** o based on a systematic review of seven randomised trials evaluating bisphosphonates for ≥ 6 months in 237 adults with CF. All trials compared bisphosphonates to placebo or control (typically vitamin D plus calcium) for 12-24 months o in adults without lung transplant ▪ bisphosphonates were associated with ▪ increased bone mineral density (BMD) at ▪ lumbar spine in analysis of 6 trials with 164 adults ▪ total hip/femur in analysis of 5 trials with 158 adults ▪ distal radius in 1 trial of 24 months duration but not in 1 trial of 6 months duration	Section 3.4.4 GPP The assessment and management of osteoporosis in patients with cystic fibrosis is complex and should be undertaken by a specialist team. The studies in the Dynamed review are from 2003 and 2004. No change required.

Reference and study type*	Information likely to be relevant	Impact on guideline
	▪ increased risk of bone pain in analysis of 6 trials with 191 adults ▪ odds ratio 18.52 (95% CI 5.39-63.57) ▪ NNH 1-12 with bone pain in 2% of control group ▪ bone pain occurred mainly with IV bisphosphonates (3 trials), but was also reported in 1 of 3 trials of oral risedronate ▪ there were no significant differences in total fractures at 1 year in analysis of 2 trials with 87 adults o comparing pamidronate IV plus oral vitamin D and calcium vs. oral vitamin D and calcium alone in 34 adults with lung transplant ▪ pamidronate IV significantly increased BMD at lumbar spine and femur ▪ there was no significant difference in number of new fractures **Aromatase inhibitors** • **risedronate may reduce anastrozole-induced bone loss in osteopenic and osteoporotic postmenopausal women at increased risk of breast cancer (level 2 [mid-level] evidence)** o based on nonclinical outcomes from substudy of IBIS-II trial, which included 1,410 postmenopausal women aged 40-70 years at increased risk of breast cancer who were randomised to anastrozole vs. placebo, then stratified and managed according to lowest baseline T score at spine or	Section 6.4.2 Risedronate is recommended to prevent vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with pre-existing vertebral fractures and/or DXA-proven osteoporosis. No specific recommendation for women at

Reference and study type*	Information likely to be relevant	Impact on guideline
	femoral neck ▪ women in stratum 1 had healthy T score (≥ -1) and were monitored ▪ women in stratum 2 had osteopenia (T score ≥ -2.5 and < -1) and were randomised to risedronate 35 mg/week vs. placebo ▪ women in stratum 3 had osteoporosis (T score > -4 and < -2.5 or had 1-2 low trauma radiographic fragility fractures) and were given risedronate 35 mg/week o 64% of participants completed study and were followed up for 3 years o in healthy or osteopenic women who had no risedronate, anastrozole was associated with decreased bone mineral density (BMD) at lumbar spine and hip (p < 0.0001 vs. placebo for each) o comparing risedronate plus anastrozole vs. placebo plus anastrozole at 3 years in women with osteopenia ▪ mean BMD at lumbar spine +1.1% vs. -2.6% (p < 0.0001) ▪ mean BMD at total hip -0.7% vs. -3.5% (p < 0.0001) o comparing anastrozole plus risedronate vs. placebo plus risedronate at 3 years in women with osteoporosis ▪ mean BMD at lumbar spine +1.2% vs. +3.9% (p = 0.006) ▪ mean BMD at total hip +0.3% vs. +1.5% (not significant) o most common adverse events included arthralgia, hot flushes, alopecia, abdominal pain, and back pain	increased risk of breast cancer.

Reference and study type*	Information likely to be relevant	Impact on guideline
	Gastrointestinal adverse effects • **zoledronic acid reported to have increased rate of discontinuation due to adverse events compared to alendronate or risedronate in patients with osteoporosis (level 3 [lacking direct] evidence)** o based on network meta-analysis with indirect comparisons of 50 studies evaluating bisphosphonates in patients with osteoporosis (44 trials compared bisphosphonate to placebo and 6 trials compared different bisphosphonate agents to each other) o the adjusted indirect analyses found increased risk of discontinuation due to adverse events with ▪ zoledronic acid compared to each of alendronate and risedronate ▪ etidronate compared to risedronate o most common adverse events were gastrointestinal related • **bisphosphonate use associated with increased risk of atypical fractures (level 2 [mid-level] evidence)** o based on two systematic reviews of ten studies (1 pooled analysis of 3 randomised trials and 9 observational studies) evaluating the association between bisphosphonate use and risk of atypical fractures in 658,497 patients. The mean patient age ranged from 70 to 80 years in all studies and most patients were women. Atypical fractures included subtrochanteric and diaphyseal fractures. Control interventions included placebo, nonbisphosphonate medication, or no treatment. The proportion of patients who had previous falls and fractures varied among studies	Section 6.4.6 includes adverse effects GPP: Bisphosphonate therapy should be evaluated every five years to determine if the benefits in continuing therapy outweigh potential risks. No action required. No recommendation in SIGN 142. Dynamed cites one additional systematic review from 2015.

Reference and study type*	Information likely to be relevant	Impact on guideline
	▪ compared to control, bisphosphonate use was associated with increased risk of atypical fractures (adjusted odds ratio 1.99, 95% CI 1.28-3.1; 7 studies, n=255,163 patients), results limited by significant heterogeneity ▪ there was consistent results for subtrochanteric (5 studies) and diaphyseal fractures (3 studies) • **use of alendronate for 5 or more years may decrease risk of hip fracture without increasing risk of atypical femur fractures compared to shorter term use in patients with osteoporosis (level 2 [mid-level] evidence)** o based on population-based cohort study of 61,990 men and women with osteoporosis (aged ≥ 50 years) starting treatment with alendronate in Denmark and followed for up to 12 years. Patients who switched to other osteoporosis drugs during follow-up were excluded from analyses o during median follow-up 6.9 years ▪ 6,784 had hip fractures (incidence rate 16.2 per 1,000 person-years) ▪ 1,428 patients had atypical femur fractures of subtrochanteric femur or femoral shaft (incidence rate 3.4 per 1,000 person-years) o in analyses adjusted for comorbidities and other medication use in previous year, there was ▪ decreased risk of hip fracture associated with ▪ longer term use of alendronate (≥ 10 years or 5-10 years) compared to shorter term use (< 5 years) ($p < 0.01$ for each) ▪ > 80% medication adherence compared to < 50% adherence ($p < 0.001$) ▪ current or recent alendronate users compared to past users ($p < 0.001$ for	

Reference and study type*	Information likely to be relevant	Impact on guideline
	each) ▪ no significant difference in risk of atypical femur fractures comparing ▪ longer term use of alendronate (≥ 10 years or 5-10 years) to shorter term use (< 5 years) ▪ patients with > 80% or 50%-80% medication adherence to patients with poor (< 50%) adherence ▪ current or recent (< 1 year prior) alendronate users to past users (≥ 1 year prior) **Osteonecrosis** • **high-dose bisphosphate therapy may be associated with high incidence of osteonecrosis of the jaw in oncology patients, but not in patients with osteoporosis** o based on 3 systematic reviews of 599 studies evaluating bisphosphate- or denosumab-associated osteonecrosis of the jaw ▪ incidence of osteonecrosis of the jaw ▪ in oncology patients, 0-12,222 cases per 100,000 patient-years for IV bisphosphates in 44 studies ▪ in patients with osteoporosis ▪ 1.04-69 cases per 100,000 patient-years for oral bisphosphates in 4 studies ▪ 0-90 cases per 100,000 patient-years for IV bisphosphates in 5	GPP: Patients starting bisphosphonates should be advised to have a dental check up as soon as possible. Dynamed cites three systematic reviews from 2015. Update on adverse events.

Reference and study type*	Information likely to be relevant	Impact on guideline
	studies **Other adverse effects** • **bisphosphonates associated with increased distal radius union time in patients with or at risk of osteoporosis (level 2 [mid-level] evidence)** o based on a systematic review of 16 studies (3 trials, 7 case series, 3 cohort, and 3 case-control studies) evaluating the association between bisphosphonates and fracture healing time in 3,558 patients with or at risk for osteoporosis (mean follow-up 84 weeks) o comparing bisphosphonates with no treatment ▪ weighted mean time to distal radius fracture union 7.45 weeks vs. 6.97 weeks ($p < 0.01$) in analysis of 2 studies ▪ weighted mean time to femur fracture union 38 weeks vs. 19 weeks (not significant) in analysis of 2 studies ▪ tibia weighted mean patient fracture union time 10.8 weeks vs. 10.38 weeks (not significant) in 1 study o there was no significant association between femoral fracture union time and duration of bisphosphonate treatment in 5 studies	Not included in SIGN 142. Outside remit.

Dynamed Plus. Osteoporosis causes and risk factors. 2017 Evidence-based summary*	**Lifestyle Factors** • **high milk intake might be associated with increased risk of fractures and mortality in women but not men** o based on a prospective cohort study including 61,433 women aged 39-74 years and 45,339 men aged 45-79 years, in Sweden, followed for mean 20.1 years o in women, milk consumption ≥ 3 glasses/day (≥ 600 g/day) associated with ▪ increased risk of fractures compared to ≤ 1 glass/day (< 200 g/day) (adjusted hazard ratio 1.16, 95% CI 1.08-1.25) ▪ increased mortality compared to ≤ 1 glass/day (< 200 g/day) (adjusted hazard ratio 1.93, 95% CI 1.80-2.06) o no significant association between milk consumption and risk of fractures or mortality in men o authors suggest the association between increased milk consumption and increased levels of biomarkers of oxidative stress (interleukin-6, 8-iso-PGF2alpha) as possible mechanism for increased risk of fractures and mortality • **lower income associated with increased BMD loss in men** o based on a cohort study of 692 men aged 30-79 years followed for 7 years o assessments included BMD and anthropometric measurements, questionnaire evaluating race and socioeconomic status, and genotyping for genetic ancestry o lower income associated with increased annualised BMD loss at femoral neck (p = 0.05), total hip (p = 0.03), and trochanter (p = 0.03) in adjusted analyses o no significant association between BMD loss and race (self-reported or genotyped ancestry)	**Section 6.3.2 Dietary-derived calcium** GPP Adequate dietary calcium consumption is recommended to meet reference intake levels of 700 mg/ day in adults. This study was not included. This could be considered for the update. Economic status was not considered in the evidence review for SIGN 142

	Altered biomarker levels o **increased high-sensitivity C-reactive protein levels associated with increased risk of fracture** ▪ based on a systematic review of eight observational studies evaluating the association of high-sensitivity C-reactive protein (CRP) levels with fracture risk in 34,840 persons with 3,407 incident fractures ▪ comparing highest CRP levels to lowest CRP levels, high CRP was associated with increased risk of fracture (relative risk 2.14, 95% CI 1.51-3.05; 6 studies) ▪ each 1 mg/L increase in CRP level was associated with a slight increase in risk of fracture (relative risk 1.17, 95% CI 1.02-1.33; 4 studies) **Gastrointestinal disorders** • **celiac disease** o **celiac disease is associated with increased risk of bone fractures** ▪ based on a systematic review of 16 observational studies evaluating the association between celiac disease and risk of bone fractures ▪ an analysis of prospective studies found that ▪ celiac disease was associated with increased risk of ▪ any fracture (odds ratio 1.3, 95% CI 1.14-1.5; 6 studies), results limited by significant heterogeneity	CRP levels are not included in SIGN 142 Dynamed evidence is from 2015: Osteoporos Int 2015 Jan;26(1):49 This could be added to risk factors, but is not likely to be relevant. Section 3.4.3 Gastrointestinal diseases Recommendation: People over the age of 50 with inflammatory bowel disease or malabsorption may be considered for fracture-risk assessment, particularly in the presence of other risk factors.

	▪ hip fracture (odds ratio 1.69, 95% CI 1.1-2.59; 4 studies), results limited by significant heterogeneity ▪ there was no significant difference in risk of in peripheral fracture in analysis of 2 studies **Other medical conditions** o **weight loss and weight gain each associated with increased fracture risk in postmenopausal women** ▪ based on post hoc analysis of patient data from the Women's Health Initiative Observational Study and Clinical Trials, which included 120,566 postmenopausal women aged 50-79 years ▪ 66% had stable weight, 15.2% lost weight and 19% gained weight in mean follow-up 11 years ▪ compared with stable weight ▪ weight loss was associated with increased risk of ▪ hip fracture (adjusted hazard ratio [HR] 1.65, 95% CI 1.5-1.8) ▪ central body fractures (adjusted HR 1.3, 95% CI 1.2-1.4) ▪ weight gain was associated with slightly increased risk of lower limb fractures (adjusted HR 1.18, 95% CI 1.12-1.25) ▪ weight loss and weight gain were each associated with small but statistically significant increase in risk of upper limb fractures ▪ • **nephrolithiasis is associated with lower bone mineral density and increased risk of osteoporosis in adults** o based on a systematic review of 28 observational studies (4	A systematic review of coeliac disease is discussed, quoting OR 1.43 This could update the evidence statement but would not change the recommendation. No change required. Section 3.3.3 Weight Provides recommendations for patients with low BMI, but does not cover weight loss or gain. Reference used by Dynamed: BMJ 2015 Jan 27;350:h25 full-text If updating, a statement on this could be included, but wouldn't make a significant difference.

	cohort studies and 24 case-control studies) evaluating bone mineral density (BMD) and risk of osteoporosis and fractures in patients with nephrolithiasis and healthy adults o nephrolithiasis was associated with ▪ lower BMD at lumbar spine (p = 0.0004, 15 studies), total hip (p = 0.04, 2 studies), and femoral neck (p = 0.03, 8 studies), results limited by significant heterogeneity ▪ increased risk of osteoporosis (odds ratio 4.12, 95% CI 3.99-4.26, 2 studies) o inconsistent results for risk of fracture ▪ nephrolithiasis was associated with increased risk of fracture (odds ratio 1.15, 95% CI 1.12-1.17, 4 case-control studies) ▪ no significant difference in analysis of 2 cohort studies, results limited by significant heterogeneity **Medications** o **loop diuretics** ▪ **loop diuretic use associated with increased risk of fracture, especially hip fracture** ▪ based on a systematic review of 4 prospective cohort and 9 case-control studies evaluating the association between loop diuretic use and fracture risk in 842,644 adults ▪ loop diuretic use was associated with increased total fracture risk (risk ratio [RR] 1.15, 95% CI 1.04-1.26; 13 studies), results limited by significant heterogeneity ▪ in subgroup analysis by fracture site ▪ loop diuretic use was associated with increased risk of hip fracture (RR 1.14, 95% CI 1.08-1.19; 11	Nephrolithiasis is not included in SIGN 142. If updating, this could be added as a risk factor. 3.5.10 Loop diuretics Concludes that evidence is unclear. New evidence is based on a systematic review from 2015 Osteoporos Int 2015 Feb;26(2):775 If updating this could be included.

	studies) ▪ no significant difference in risk of lower arm or wrist fractures in analysis of 3 studies • inconsistent evidence for risk of fractures with anticoagulation o **low-molecular-weight heparin use for 3 or more months may not increase risk of fracture at 6-12 months in patients with underlying comorbidities (level 2 [mid-level] evidence)** ▪ based on a systematic review, limited by clinical heterogeneity, of 16 studies (10 randomised trials and 4 cohort studies) evaluating the association between long-term (≥ 3 months) low-molecular-weight heparin (LMWH) use and risk of fracture in 4,865 nonpregnant adults with comorbidities ▪ control interventions and underlying comorbidities varied across studies ▪ no significant difference in risk of fractures at 6-12 months comparing LMWH for 3-6 months to unfractionated heparin, oral vitamin K antagonist, or placebo in analysis of 5 studies with 2,280 patients with venous thromboembolism and underlying cardiovascular disease or cancer • **zolpidem use associated with increased risk of fractures (level 2 [mid-level] evidence)** o based on a systematic review of 9 observational studies (4 cohort, 4 case-control, and 1 case-crossover) evaluating zolpidem use and risk of fractures in 1,092,925 adults o zolpidem was associated with an increased risk of ▪ any fracture (relative risk [RR] 1.92, 95% CI 1.65-2.24; 9 studies n = 1,092,925 adults), results limited by significant heterogeneity	Section 3.5.1 The guideline states: The association between low molecular weight heparin use and fracture rate has not been adequately addressed by research. Dynamed cites an SR from 2016 If updating for other reasons, this could be included, but it is not likely to have a significant impact. Not included in SIGN 142 This needs to be included now. 3.5 Section 3.5.14 Antidiabetic agents Recommendation: People aged over 50 using

	▪ hip fracture (RR 2.8 95% CI 2.19-3.58; 4 studies) • **risk of osteoporotic fracture may be increased with use of insulin, sulfonylureas, or thiazolidinediones, but not metformin or sitagliptin (level 2 [mid-level] evidence)** o based on a prospective cohort study including 72,738 adults (mean age 52 years) with type 2 diabetes who were new users of antidiabetic drugs (12% were new sitagliptin users, of whom 86% were also on metformin) and followed for up to 6 years o the overall incidence of major osteoporotic fracture (hip, clinical spine, proximal humerus, or distal radius fracture) was 4.1 fractures per 1,000 person-years during median follow-up 2.2 years o incidence of major osteoporotic fractures per 1,000 person-years was 4.8 in sitagliptin users compared with 4 in nonusers (adjusted hazard ratio [HR] 1.1, 95% CI 0.8-1.4) o there was consistent results for metformin o antidiabetic drugs were associated with an increased risk of major osteoporotic fracture: ▪ insulin (adjusted HR 2.1, 95% CI 1.6-2.8) ▪ sulfonylureas (adjusted HR 1.3, 95% CI 1.1-1.5) ▪ thiazolidinediones (adjusted HR 1.2, 1.04-1.5) **Risk Prediction** **Commonly used and validated calculators** • **FRAX without bone mineral density and Osteoporosis Self-Assessment Screening Tool may each help identify elderly persons at low risk who may not require bone mineral density testing during osteoporosis screening (level 2 [mid-level] evidence)** o based on a prognostic cohort study carried out without independent validation on 626 persons aged ≥ 70 years (mean age 78 years, 55% male) who had dual-energy x-ray absorptiometry screening and were assessed for risk of	TZDs are at higher fracture risk than people with diabetes who are treated with other agents and should be considered for fracture-risk assessment, particularly in the presence of other risk factors. J Clin Endocrinol Metab 2016 May;101(5):1963 full-text This should be included in an update. Section 4.2 Recommendation: Fracture-risk assessment should be carried out, preferably using QFracture, prior to DXA in patients with clinical risk factors for osteoporosis and in whom antiosteoporosis treatment is being considered. This could be included in an update.

	major osteoporotic fracture by 2 prediction tools ▪ FRAX without bone mineral density (BMD) ▪ Osteoporosis Self-Assessment Screening Tool (OST) o osteoporosis was defined as a T-score < -2.5, while the reference standard was osteoporosis defined by bone mineral density testing of lumbar spine, femoral neck, total hip, worst hip (femoral neck or total hip), and worst overall site. The following threshold scores for each prediction tool were derived to identify persons at low risk of osteoporosis: ▪ ≤ 3% on FRAX without BMD 10-year hip fracture risk score ▪ ≤ 6% on FRAX without BMD 10-year major osteoporotic fracture risk score ▪ 0 on OST score o based on these thresholds, BMD testing rates would be reduced by 33%-36% in persons being screened for osteoporosis, with 7.8%-10.4% of osteoporosis cases being missed o for prediction of osteoporosis (ranges indicate performance based on BMD measurements at different sites) ▪ FRAX 10-year risk of hip fracture score with cutoff 3% had sensitivity 81.3%-92.2% and specificity 34.3%-37.1% ▪ FRAX 10-year risk of major osteoporotic fracture score with cutoff 6% had sensitivity 87.5%-94.1% and specificity 35%-37.1% ▪ OST with cutoff 0 had sensitivity 90.6%-94.1% and specificity 37.5%-39.9% • **QFracture and FRAX (without bone mineral density) tools each have better performance than Garvan (without bone mineral density) tool for predicting risk of hip fracture in adults ≥ 50 years old (level 1 [likely reliable] evidence)** o based on a cohort study of 1,054,815 adults aged 50-90 years in Israel. The study assessed for risk of fracture using	

	QFracture, FRAX (without bone mineral density), and Garvan (without bone mineral density) tools and participants were followed for 5 years. Results showed that 2.7% had hip fracture and 7.7% had major osteoporotic fracture (during mean follow-up of 4.7 years) o among patients in highest (top 10%) risk category ▪ predictive performance for hip fracture ▪ QFracture with cutoff score 4 had sensitivity 45.1% and specificity 91% ▪ FRAX with cutoff score 1.8 had sensitivity 43.6% and specificity 90.9% ▪ Garvan with cutoff score 2.7 had sensitivity 36.9% and specificity 90.7% ▪ predictive performance for major osteoporotic fracture ▪ QFracture with cutoff score 6.7 had sensitivity 26.7% and specificity 91.4% ▪ FRAX with cutoff score 8.5 had sensitivity 29% and specificity 91.6% o among patients in second highest (top 20%) risk category, all 3 prediction tools had higher sensitivity (by about 20%) but lower specificity (by about 10%) for prediction of both hip and major osteoporotic fractures o for prediction of hip fracture, QFracture associated with significantly higher discrimination (c-statistic 82.7%) compared to each of FRAX (c-statistic 81.5%) and Garvan tools (c-statistic 77.8%) and FRAX associated with significantly higher discrimination than Garvan tool o both QFracture and FRAX had moderate discrimination for prediction of major osteoporotic fracture (c-statistic 71% for each) **Risk prediction in women** • **Osteoporosis Self-Assessment Tool and Osteoporosis Self-**	

	Assessment Tool for Asians may have moderate sensitivity and low specificity for detection of osteoporosis in postmenopausal women (level 2 [mid-level] evidence) o based on a systematic review of 108 diagnostic cohort studies evaluating clinical risk assessment tools for detection of osteoporosis ▪ clinical risk assessment tools included Osteoporosis Self-Assessment Tool (OST, 55 studies), Simple Calculated Osteoporosis Risk Estimation (SCORE, 32 studies), Osteoporosis Self-Assessment Tool for Asians (OSTA, 27 studies), Osteoporosis Risk Assessment Instrument (26 studies), and body weight criteria (15 studies) ▪ 78 studies included only women, 24 studies included only men and 6 studies included both o osteoporosis prevalence ranged from 4.1% to 44.8% by dual energy x-ray absorptiometry scan (T-score ≤ −2.5) at femoral neck, total hip, or lumbar spine o most analyses were limited by significant statistical heterogeneity. The pooled diagnostic performance of OST with cutoff < 1 for detection of osteoporosis at femoral neck in analysis of 3 studies with 31,779 postmenopausal women in the United States ▪ sensitivity 89% (95% CI 82%-96%); specificity 41% (95% CI 23%-59%) o pooled diagnostic performance of OSTA in postmenopausal women in Thailand ▪ OSTA with cutoff ≤ 1 for detection of osteoporosis at ▪ femoral neck in analysis of 8 studies with 3,079 women ▪ sensitivity 84% (95% CI 76%-92%); specificity 61% (95% CI 50%-72%) ▪ lumbar spine in analysis of 7 studies with	

	2,780 women ▪ sensitivity 71% (95% CI 60%-82%); specificity 62% (95% CI 52%-73%) ▪ OSTA with cutoff ≤ 0 for detection of osteoporosis at ▪ femoral neck in analysis of 3 studies with 1,201 postmenopausal women ▪ sensitivity 90% (95% CI 84%-95%); specificity 47% (95% CI 30%-64%) ▪ lumbar spine in analysis of 3 studies with 1,201 postmenopausal women in Thailand ▪ sensitivity 83% (95% CI 67%-99%); specificity 48% (95% CI 36%-60%) o meta-analyses for other clinical risk assessment tools were not performed due to insufficient data • **Osteoporosis Self-Assessment Tool may have moderate sensitivity and low specificity for detection of osteoporosis in men (level 2 [mid-level] evidence)** o based on a systematic review of 108 diagnostic cohort studies evaluating clinical risk assessment tools for detection for osteoporosis ▪ clinical risk assessment tools included Osteoporosis Self-Assessment Tool (OST, 55 studies), Simple Calculated Osteoporosis Risk Estimation (SCORE, 32 studies), Osteoporosis Self-Assessment Tool for Asians (OSTA, 27 studies), Osteoporosis Risk Assessment Instrument (26 studies), and body weight criteria (15 studies) ▪ 78 studies included only women, 24 studies included only men and 6 studies included both o osteoporosis prevalence ranged from 4.1% to 44.8% by DXA scan (T-score ≤ −2.5) at femoral neck, total hip or lumbar spine o all analyses were limited by significant statistical	

	heterogeneity o pooled diagnostic performance of OST for detection of osteoporosis at femoral neck, total hip or lumbar spine in analysis of men in United States showed ▪ OST with cutoff = 3 in analysis of 3 studies with 760 men ▪ sensitivity 88% (95% CI 79%-97%); specificity 55% (95% CI 42%-68%) ▪ OST with cutoff = 2 in analysis of 3 studies with 5,250 men ▪ sensitivity 81% (95% CI 70%-92%); specificity 54% (95% CI 32%-76%) ▪ OST with cutoff = 1 in analysis of 3 studies with 5,250 men ▪ sensitivity 73% (95% CI 62%-84%); specificity 64% (95% CI 45%-83%) o meta-analyses for other clinical risk assessment tools were not performed due to insufficient data	
BMJ Best Practice. Osteoporosis. 2017 Best practice report*	**Summary** • Asymptomatic until fracture occurs. • Diagnosis based on history of prior fragility fracture or low bone mineral density (BMD), which is defined as a T-score ≤-2.5. • Screening is based on individual risk factors, including female gender, maternal history of fragility fracture/osteoporosis, older age, low body mass index (<20 to 25 kg/m^2), body weight <58 kg, weight loss of >10% of body weight, androgen deprivation treatment (in males), aromatase inhibitor treatment (in females), corticosteroid use, tobacco use, and kidney stone disease. • Fall prevention is first-line therapy. • Bisphosphonates are first-line pharmacological therapy for postmenopausal women and men. • In postmenopausal women, oestrogen is considered only for those at high risk for whom nonoestrogen medicines are	SIGN 142 *Table 2: Risk factors associated with fragility fracture which should prompt consideration of fracture-risk assessment* does not include, gender, body weight, androgen deprivation. This is already covered. No new data.

	inappropriate.	
BMJ Best Practice. Osteoporotic spinal compression fractures. 2017 Best practice report*	**Summary** • Most are isolated fractures of the anterior spinal column related to low bone mineral density. • They are associated with significant performance impairments in physical, functional, and psychosocial domains. • Postmenopausal women and patients taking long-term corticosteroid therapy are most susceptible. • The causative mechanism is a combination of flexion and axial compression loading. • It is important to exclude the possibility of pathological fracture due to malignancy or infection. • Treatment frequently involves pain relief, temporary use of an orthosis (e.g., Jewett/Lumbar brace or thoracolumbosacral orthosis) and walking aids (e.g., stick, elbow crutches, all-terrain rollator). • Radiographic and clinical follow-up is required every 6 weeks for 3 months post-injury.	Outside remit of the guideline.
Dynamed Plus. Calcium and vitamin D for treatment and prevention of osteoporosis. 2015 Evidence-based summary*	**Recommendations** **Vitamin D in postmenopausal women** • **vitamin D3 at high dose twice monthly or at low dose daily is not associated with improved function or reduced falls in postmenopausal women with vitamin D insufficiency (level 2 [mid-level] evidence)** o based on randomised trial (with unclear method as regards randomisation and allocation concealment) of 230 postmenopausal women ≤ 75 years old (mean age 61 years) with 25-hydroxyvitamin D (25[OH]D) levels 14-27 ng/mL (35-67 nmol/L) and without osteoporosis that were randomised	**SIGN 142:** GPP: In Scotland, dietary vitamin D intakes are insufficient to meet the needs of people with inadequate sunlight exposure. Supplementation with 10 micrograms/day of vitamin D (400 IU) should be considered to avoid deficiency. New evidence emerging on vitamin D so should be updated.

	to 1 of 3 interventions for 1 year ▪ cholecalciferol loading dose of 50,000 units/day (1,250 mcg/day) for 15 days then 50,000 units (1,250 mcg) every 15th day (high-dose vitamin D3) ▪ cholecalciferol 800 units/day (20 mcg/day) (low-dose vitamin D3) ▪ placebo o women were counseled to consume 600-1,400 mg/day calcium by diet and/or supplemental calcium o 96% of participants completed trial. The high-dose vitamin D treatment arm achieved and maintained 25(OH)D levels ≥ 30 ng/mL (75 nmol/L) o mean 25-hydroxyvitamin D levels from day 30-365 ($p < 0.001$ across groups, no pairwise p values reported) was: ▪ 56 ng/mL (140 nmol/L) with high-dose vitamin D3 ▪ 28 ng/mL (70 nmol/L) with low-dose vitamin D3 ▪ 19 ng/mL (47 nmol/L) with placebo o there were no significant differences between groups at 12 months in ▪ functional status (assessed by Health Assessment Questionnaire) ▪ total falls, falls per patient, or fractures ▪ Timed Up and Go Test, Five Sit-to-Stand Test, or physical activity (assessed by Physical Activity Scale for the Elderly) ▪ bone mineral density (lumbar spine, hip, femoral neck, or total-body), trabecular bone score, or muscle mass o high-dose vitamin D3 associated with significantly greater total fractional calcium absorption at 1 year (adjusted for baseline calcium absorption) compared with both low-dose vitamin D3 and placebo • **calcium plus vitamin D supplementation might reduce hip fractures in women taking hormone therapy but not in women not taking hormone therapy (level 2 [mid-level] evidence)**	SIGN 142 Rec: Calcium and vitamin D supplements may be considered to reduce the risk of non-vertebral fractures in patients who are at risk of

	o based on subgroup analysis of a randomised trial (WHI CaD) of 16,089 postmenopausal women who were randomized to 1 of 4 groups and followed up for an average of 7.2 years: ▪ calcium plus vitamin D supplementation with hormone therapy ▪ calcium plus vitamin D supplementation without hormone therapy ▪ hormone therapy without supplementation ▪ placebo (no supplementation or hormone therapy) o hip fracture rates comparing calcium plus vitamin D supplementation vs. no supplementation: ▪ 0.77% vs. 1.28% in women taking hormone therapy (hazard ratio for hip fracture 0.59, 95% CI 0.38-0.93) ▪ 1.74% vs. 1.54% in women not taking hormone therapy (not significant) **Older Adults (men and women combined)** **Calcium in older adults** • **calcium supplementation has inconsistent evidence to suggest it reduces overall fracture risk in adults > 50 years old (level 2 [mid-level] evidence)** o based on a systematic review of 28 randomised trials and 55 cohort studies evaluating dietary calcium or calcium supplements for fracture prevention in adults > 50 years old ▪ 26 randomised trials and 11 cohort studies evaluated calcium supplements (including 4 high-quality trials) ▪ 2 randomised trials and 44 cohort studies evaluated dietary calcium o comparing calcium supplements to control ▪ calcium supplements were associated with ▪ reduced risk of any fracture in analysis of 20 trials with 58,573 adults ▪ relative risk (RR) 0.89 (95% CI	deficiency due to insufficient dietary intake or limited sunlight exposure. Include in update on vitamin D. Based on systematic reviews from 2015 to 2016. Unlikely to change recommendation.

	0.81-0.96) ▪ NNT 44-209 with any fracture in 12% of control groups ▪ there was no significant difference in overall risk of fracture in an analysis limited to 4 high-quality trials with 44,505 patients ▪ no significant reduction in risk of vertebral fracture (RR 0.89, 95% CI 0.75-1.06) in analysis of 4 high-quality trials ▪ no significant difference in risk of hip fracture in analysis of 13 trials with 56,648 patients o meta-analysis was not performed for effects of dietary calcium o comparing dietary calcium to control in cohort studies ▪ no significant associations between levels of dietary calcium intake and fracture risk was found for ▪ any fracture in 14 of 22 studies ▪ vertebral fracture in 7 of 8 studies ▪ hip fracture in 17 of 21 studies ▪ forearm fracture in 5 of 7 studies ▪ increased dietary calcium intake was associated with reduced risk of fracture in 13 studies and increased risk of fracture in 1 study **Vitamin D in older adults** • **vitamin D alone does not reduce fracture risk in older adults (level 1 [likely reliable] evidence)** o based on a systematic review of 53 randomised or quasi-randomised trials evaluating vitamin D or vitamin D analogs alone or with calcium, and reporting fracture outcomes in 91,791 adults > 65 years old. The trials were conducted in community, nursing home and hospital settings o comparing vitamin D to placebo or no treatment, there were	New evidence does not change the recommendation in SIGN 142. No action required.

	no significant differences in ▪ any new fracture in analysis of 15 trials with 28,271 patients ▪ new hip fracture in analysis of 11 trials with 27,693 patients ▪ new nonvertebral fracture in analysis of 12 trials with 22,930 patients ▪ new vertebral fracture or deformity in analysis of 6 trials with 11,396 patients • **vitamin D supplementation does not appear to increase bone mineral density in older adults, except possibly in femoral neck (level 3 [lacking direct] evidence)** o based on a systematic review of 23 trials comparing vitamin D supplementation to control in 4,082 older adults (mean age 59 years, 92% women). The review did not report on the quality assessment of individual trials. Control treatments included placebo, no treatment or lower dose vitamin D supplement o there were no significant differences in bone mineral density in ▪ lumbar spine in analysis of 17 studies ▪ total hip/trochanter in analysis of 15 studies, results limited by significant heterogeneity ▪ total body in analysis of 8 studies, results limited by significant heterogeneity ▪ forearm in analysis of 6 studies o vitamin D supplementation was associated with increased bone mineral density in femoral neck (weighted mean difference 0.8%, 95% CI 0.2%-1.4%; 13 studies) **Calcium plus vitamin D in older adults** • **calcium plus vitamin D supplementation appears to reduce fractures in older adults (level 2 [mid-level] evidence)** o based on 4 systematic reviews with some inconsistency	No action required. New evidence unlikely to change the existing

	o **vitamin D plus calcium may reduce rate of nonvertebral fractures in older adults (level 2 [mid-level] evidence)** ▪ based on a systematic review of 53 randomised or quasi-randomised trials evaluating vitamin D or vitamin D analogs alone or with calcium, and reporting fracture outcomes in 91,791 adults > 65 years old ▪ the trials were conducted in community, nursing home and hospital settings, and most trials had ≥ 1 limitation including ▪ unclear or no allocation concealment ▪ lack of or unclear blinding ▪ baseline differences ▪ differences in management ▪ comparing vitamin D plus calcium to placebo or no treatment (control), ▪ vitamin D plus calcium was associated with reduction in new nonvertebral fracture in analysis of 8 trials with 10,380 patients ▪ risk ratio (RR) 0.86 (95% CI 0.78-0.96); NNT 38-209 with new nonvertebral fracture in 12% of control group ▪ statistically significant (RR 0.84, 95% CI 0.74-0.95) in subgroup analysis of 5 trials with 7,560 patients not selected on basis of previous osteoporotic fracture ▪ not significant (RR 0.93, 95% CI 0.77-1.13) in subgroup analysis of 3 trials with 2,820 patients selected on basis of previous osteoporotic fracture ▪ vitamin D plus calcium was associated with reduction in new hip fracture in analysis of 9 trials with 49,853 patients	recommendation.

	▪ RR 0.84 (95% CI 0.74-0.96); NNT 210-1,364 with new hip fracture in 1.8% of control group ▪ statistically significant in subgroup analysis of 2 trials with 3,853 patients in nursing home or residential care facility ▪ RR 0.75 (95% CI 0.62-0.92; NNT 24-114 with new hip fracture in 11% of control group ▪ not significant (RR 0.91, 95% CI 0.77-1.09) in analysis of 7 trials with 46,000 community-dwelling older adults ▪ statistically significant (RR 0.82, 95% CI 0.71-0.94) in subgroup analysis of 5 trials with 43,719 patients not selected on basis of previous osteoporotic fracture ▪ not significant (RR 1.02, 95% CI 0.71-1.47) in subgroup analysis of 4 trials with 6,134 patients selected on basis of previous osteoporotic fracture ▪ no significant differences in new vertebral fracture (RR 0.89, 95% CI 0.74-1.09) in analysis of 4 trials with 42,185 patients ▪ vitamin D with or without calcium (compared to placebo or calcium alone) was not associated with increased mortality (RR 0.97, 95% CI 0.93-1.01) in analysis of 29 trials with 71,032 participants ▪ vitamin D with or without calcium (compared to placebo or calcium alone) associated with increased adverse effects including	

	▪ hypercalcemia (RR 2.28, 95% CI 1.57-3.31) in analysis of 21 trials with 17,124 patients, particularly with calcitriol (4 trials with 988 patients) ▪ renal disease (RR 1.16, 95% CI 1.02-1.33) in analysis of 11 trials with 46,548 patients **Patients taking corticosteroids** • **addition of calcium plus vitamin D3 to prednisolone therapy may increase bone mineral content in children with new-onset nephrotic syndrome (level 3 [lacking direct] evidence)** o based on a small randomised trial of 45 prepubertal children (mean age 4 years) in India taking prednisolone for new-onset nephrotic syndrome that were randomised to calcium 500 mg/day orally plus vitamin D3 1,000 units/day (25 mcg/day) orally vs. no treatment and followed up for 12 weeks. Bone mineral content and density were measured at lumbar spine o comparing calcium plus vitamin D3 vs. no treatment: ▪ mean change in bone mineral content +11.2% vs. -8.9% ($p < 0.0001$) ▪ mean increase in bone mineral density 2.8% vs. 0.74% (not significant)	Evidence is unlikely to support a recommendation in a SIGN guideline. No action required.

Section 3: Consultation feedback

Former members of the SIGN 142 guideline development group, and three additional clinicians were invited to comment on the report and the proposed areas for update.

Reviewer	Comments
Dr Stephen Gallacher, Consultant Physician & Endocrinologist, NHS Greater Glasgow and Clyde	I would agree with the proposal here and would support those section marked as desirable/essential. I think the issue on long term denosumab safety is very important. As a smaller issue there is now evidence accruing that HIV and some anti-retroviral therapies might be associated with an increase in fracture risk
Dr Ailsa E Gebbie, Consultant Gynaecologist, NHS Lothian	There is not much new in my area of expertise which relates to hormonal contraception in 3.5.8. Certainly no change to recommendations at all related to contraceptive use and osteoporosis.
Dr Andrew Duckworth, Consultant Orthopaedic Trauma Surgeon, NHS Lothian	I agree completely with your assessment of the scoping results and the areas suggested for update, which all seem relevant. The only area I think may be considered for updating would be regarding atypical femoral fractures and bisphosphonate use. I have attached some references that may be relevant (the 2010 would not be picked up but I was not sure if this was included in previous reviews). I understand the limitation regarding this area is the lack of evidence, but I think it certainly is an area that requires some attention if possible. Refs: N Engl J Med. 2010 May 13;362(19):1761-71. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. Black DM[1], Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, Cauley J, Leung PC, Boonen S, Santora A, de Papp A, Bauer DC; Fracture Intervention Trial Steering Committee; HORIZON Pivotal Fracture Trial Steering Committee. Fam Pract. 2015 Jun;32(3):276-81. Increased risk for atypical fractures associated with bisphosphonate use. Lee S[1], Yin RV[2], Hirpara H[2], Lee NC[2], Lee A[2], Llanos S[3], Phung OJ[4].

	Acta Orthop. 2015 Feb;86(1):100-7. Risk of atypical femoral fracture during and after bisphosphonate use. Schilcher J[1], Koeppen V, Aspenberg P, Michaëlsson K.